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(54) Title: NUCLEIC ACID MOLECULES AND PROTEINS FOR THE IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF OVARIAN CANCER

(57) Abstract: The invention relates to newly discovered nucleic acid molecules and proteins associated with ovarian cancer. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human ovarian cancers are provided.



WO 02/071928 A2

- 1 -

NUCLEIC ACID MOLECULES AND PROTEINS FOR THE IDENTIFICATION,
ASSESSMENT, PREVENTION, AND THERAPY OF
OVARIAN CANCER

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RELATED APPLICATIONS

The present application claims priority from U.S. provisional patent application serial no. 60/276,025, filed on March 14, 2001, which was abandoned on September 25, 2001, and from U.S. provisional patent application serial no. 60/325,149, filed on September 26, 2001. The present application also claims priority from U.S. provisional
10 patent application serial no. 60/276,026, filed on March 14, 2001, which was abandoned on September 25, 2001, and from U.S. provisional patent application serial no. 60/324,967, filed September 26, 2001. The present application additionally claims priority from U.S. provisional patent application serial no. 60/311,732, filed August 10, 2001, which was abandoned on September 25, 2001, and from U.S. provisional patent
15 application serial no. 60/325,102, filed September 26, 2001. The present application also claims priority from U.S. provisional patent application serial no. 60/323,580, filed September 19, 2001. All of the above applications are expressly incorporated by reference.

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FIELD OF THE INVENTION

The field of the invention is ovarian cancer, including diagnosis, characterization, management, and therapy of ovarian cancer.

BACKGROUND OF THE INVENTION

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Ovarian cancer is responsible for significant morbidity and mortality in populations around the world. Ovarian cancer is classified, on the basis of clinical and pathological features, in three groups, namely epithelial ovarian cancer (EOC; >90% of ovarian cancer in Western countries), germ cell tumors (*circa* 2-3% of ovarian cancer), and stromal ovarian cancer (*circa* 5% of ovarian cancer; Ozols *et al.*, 1997, *Cancer*
30 *Principles and Practice of Oncology*, 5th ed., DeVita *et al.*, Eds. pp. 1502). Relative to EOC, germ cell tumors and stromal ovarian cancers are more easily detected and treated

- 2 -

at an early stage, translating into higher/better survival rates for patients afflicted with these two types of ovarian cancer.

There are numerous types of ovarian tumors, some of which are benign, and others of which are malignant. Treatment (including non-treatment) options and predictions of patient outcome depend on accurate classification of the ovarian cancer. Ovarian cancers are named according to the type of cells from which the cancer is derived and whether the ovarian cancer is benign or malignant. Recognized histological tumor types include, for example, serous, mucinous, endometrioid, and clear cell tumors. In addition, ovarian cancers are classified according to recognized grade and stage scales.

In grade I, the tumor tissue is well differentiated. In grade II, tumor tissue is moderately well differentiated. In grade III, the tumor tissue is poorly differentiated. This grade correlates with a less favorable prognosis than grades I and II. Stage I is generally confined within the capsule surrounding one (stage IA) or both (stage IB) ovaries, although in some stage I (*i.e.* stage IC) cancers, malignant cells may be detected in ascites, in peritoneal rinse fluid, or on the surface of the ovaries. Stage II involves extension or metastasis of the tumor from one or both ovaries to other pelvic structures. In stage IIA, the tumor extends or has metastasized to the uterus, the fallopian tubes, or both. Stage IIB involves extension of the tumor to the pelvis. Stage IIC is stage IIA or IIB in which malignant cells may be detected in ascites, in peritoneal rinse fluid, or on the surface of the ovaries. In stage III, the tumor comprises at least one malignant extension to the small bowel or the omentum, has formed extrapelvic peritoneal implants of microscopic (stage IIIA) or macroscopic (< 2 centimeter diameter, stage IIIB; > 2 centimeter diameter, stage IIIC) size, or has metastasized to a retroperitoneal or inguinal lymph node (an alternate indicator of stage IIIC). In stage IV, distant (*i.e.* non-peritoneal) metastases of the tumor can be detected.

The durations of the various stages of ovarian cancer are not presently known, but are believed to be at least about a year each (Richart *et al.*, 1969, *Am. J. Obstet. Gynecol.* 105:386). Prognosis declines with increasing stage designation. For example, 5-year survival rates for patients diagnosed with stage I, II, III, and IV ovarian cancer are 80%, 57%, 25%, and 8%, respectively.

Despite being the third most prevalent gynecological cancer, ovarian cancer is the leading cause of death among those afflicted with gynecological cancers. The disproportionate mortality of ovarian cancer is attributable to a substantial absence of symptoms among those afflicted with early-stage ovarian cancer and to difficulty
5 diagnosing ovarian cancer at an early stage. Patients afflicted with ovarian cancer most often present with non-specific complaints, such as abnormal vaginal bleeding, gastrointestinal symptoms, urinary tract symptoms, lower abdominal pain, and generalized abdominal distension. These patients rarely present with paraneoplastic symptoms or with symptoms which clearly indicate their affliction. Presently, less than
10 about 40% of patients afflicted with ovarian cancer present with stage I or stage II. Management of ovarian cancer would be significantly enhanced if the disease could be detected at an earlier stage, when treatments are much more generally efficacious.

Ovarian cancer may be diagnosed, in part, by collecting a routine medical history from a patient and by performing physical examination, x-ray examination, and
15 chemical and hematological studies on the patient. Hematological tests which may be indicative of ovarian cancer in a patient include analyses of serum levels of proteins designated CA125 and DF3 and plasma levels of lysophosphatidic acid (LPA). Palpation of the ovaries and ultrasound techniques (particularly including endovaginal ultrasound and color Doppler flow ultrasound techniques) can aid detection of ovarian
20 tumors and differentiation of ovarian cancer from benign ovarian cysts. However, a definitive diagnosis of ovarian cancer typically requires performing exploratory laparotomy of the patient.

Potential tests for the detection of ovarian cancer (*e.g.*, screening, reflex or monitoring) may be characterized by a number of factors. The "sensitivity" of an
25 assay refers to the probability that the test will yield a positive result in an individual afflicted with ovarian cancer. The "specificity" of an assay refers to the probability that the test will yield a negative result in an individual not afflicted with ovarian cancer. The "positive predictive value" (PPV) of an assay is the ratio of true positive results (*i.e.* positive assay results for patients afflicted with ovarian cancer) to all positive results
30 (*i.e.* positive assay results for patients afflicted with ovarian cancer + positive assay results for patients not afflicted with ovarian cancer). It has been estimated that in order for an assay to be an appropriate population-wide screening tool for ovarian cancer the

assay must have a PPV of at least about 10% (Rosenthal *et al.*, 1998, *Sem. Oncol.* 25:315-325). It would thus be desirable for a screening assay for detecting ovarian cancer in patients to have a high sensitivity and a high PPV. Monitoring and reflex tests would also require appropriate specifications.

5 Owing to the cost, limited sensitivity, and limited specificity of known methods of detecting ovarian cancer, screening is not presently performed for the general population. In addition, the need to perform laparotomy in order to diagnose ovarian cancer in patients who screen positive for indications of ovarian cancer limits the desirability of population-wide screening, such that a PPV even greater than 10%
10 would be desirable.

 Prior use of serum CA125 level as a diagnostic marker for ovarian cancer indicated that this method exhibited insufficient specificity for use as a general screening method. Use of a refined algorithm for interpreting CA125 levels in serial retrospective samples obtained from patients improved the specificity of the method
15 without shifting detection of ovarian cancer to an earlier stage (Skakes, 1995, *Cancer* 76:2004). Screening for LPA to detect gynecological cancers including ovarian cancer exhibited a sensitivity of about 96% and a specificity of about 89%. However, CA125-based screening methods and LPA-based screening methods are hampered by the presence of CA125 and LPA, respectively, in the serum of patients afflicted with
20 conditions other than ovarian cancer. For example, serum CA125 levels are known to be associated with menstruation, pregnancy, gastrointestinal and hepatic conditions such as colitis and cirrhosis, pericarditis, renal disease, and various non-ovarian malignancies. Serum LPA is known, for example, to be affected by the presence of non-ovarian gynecological malignancies. A screening method having a greater specificity for
25 ovarian cancer than the current screening methods for CA125 and LPA could provide a population-wide screening for early stage ovarian cancer.

 Presently greater than about 60% of ovarian cancers diagnosed in patients are stage III or stage IV cancers. Treatment at these stages is largely limited to cytoreductive surgery (when feasible) and chemotherapy, both of which aim to slow the
30 spread and development of metastasized tumor. Substantially all late stage ovarian cancer patients currently undergo combination chemotherapy as primary treatment, usually a combination of a platinum compound and a taxane. Median survival for

responding patients is about one year. Combination chemotherapy involving agents such as doxorubicin, cyclophosphamide, cisplatin, hexamethylmelamine, paclitaxel, and methotrexate may improve survival rates in these groups, relative to single-agent therapies. Various recently-developed chemotherapeutic agents and treatment regimens have also demonstrated usefulness for treatment of advanced ovarian cancer. For example, use of the topoisomerase I inhibitor topectan, use of amifostine to minimize chemotherapeutic side effects, and use of intraperitoneal chemotherapy for patients having peritoneally implanted tumors have demonstrated at least limited utility. Presently, however, the 5-year survival rate for patients afflicted with stage III ovarian cancer is 25%, and the survival rate for patients afflicted with stage IV ovarian cancer is 8%.

In summary, the earlier ovarian cancer is detected, the aggressiveness of therapeutic intervention and the side effects associated with therapeutic intervention are minimized. More importantly, the earlier the cancer is detected, the survival rate and quality of life of ovarian cancer patients is enhanced. Thus, a pressing need exists for methods of detecting ovarian cancer as early as possible. There also exists a need for methods of detecting recurrence of ovarian cancer as well as methods for predicting and monitoring the efficacy of treatment. There further exists a need for new therapeutic methods for treating ovarian cancer. The present invention satisfies these needs.

20

SUMMARY OF THE INVENTION

The invention relates to cancer markers (hereinafter “markers” or “markers of the inventions”), which are listed in Tables 1-3. The invention provides nucleic acids and proteins that are encoded by or correspond to the markers (hereinafter “marker nucleic acids” and “marker proteins,” respectively). The invention further provides antibodies, antibody derivatives and antibody fragments which bind specifically with such proteins and/or fragments of the proteins.

In one aspect, the invention relates to various diagnostic, monitoring, test and other methods related to ovarian cancer detection and therapy. In one embodiment, the invention provides a diagnostic method of assessing whether a patient has ovarian cancer or has higher than normal risk for developing ovarian cancer, comprising the steps of comparing the level of expression of a marker of the invention in a patient

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sample and the normal level of expression of the marker in a control, *e.g.*, a sample from a patient without ovarian cancer. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with ovarian cancer or has higher than normal risk for developing ovarian cancer.

In a preferred embodiment of the diagnostic method, the marker is over-expressed by at least two-fold in at least about 20% of stage I ovarian cancer patients, stage II ovarian cancer patients, stage III ovarian cancer patients, stage IV ovarian cancer patients, grade I ovarian cancer patients, grade II ovarian cancer patients, grade III ovarian cancer patients, epithelial ovarian cancer patients, stromal ovarian cancer patients, germ cell ovarian cancer patients, malignant ovarian cancer patients, benign ovarian cancer patients, serous neoplasm ovarian cancer patients, mucinous neoplasm ovarian cancer patients, endometrioid neoplasm ovarian cancer patients and/or clear cell neoplasm ovarian cancer patients.

The diagnostic methods of the present invention are particularly useful for patients with an identified pelvic mass or symptoms associated with ovarian cancer. The methods of the present invention can also be of particular use with patients having an enhanced risk of developing ovarian cancer (*e.g.*, patients having a familial history of ovarian cancer, patients identified as having a mutant oncogene, and patients at least about 50 years of age).

In a preferred diagnostic method of assessing whether a patient is afflicted with ovarian cancer (*e.g.*, new detection ("screening"), detection of recurrence, reflex testing), the method comprises comparing:

- a) the level of expression of a marker of the invention in a patient sample, and
- b) the normal level of expression of the marker in a control non-ovarian cancer sample.

A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with ovarian cancer.

The invention also provides diagnostic methods for assessing the efficacy of a therapy for inhibiting ovarian cancer in a patient. Such methods comprise comparing:

- 5 a) expression of a marker of the invention in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, and
- b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy.

A significantly lower level of expression of the marker in the second sample relative to
10 that in the first sample is an indication that the therapy is efficacious for inhibiting ovarian cancer in the patient.

It will be appreciated that in these methods the “therapy” may be any therapy for treating ovarian cancer including, but not limited to, chemotherapy, radiation therapy, surgical removal of tumor tissue, gene therapy and biologic therapy such as the
15 administering of antibodies and chemokines. Thus, the methods of the invention may be used to evaluate a patient before, during and after therapy, for example, to evaluate the reduction in tumor burden.

In a preferred embodiment, the diagnostic methods of the present invention are directed to therapy using a chemical or biologic agent. These methods
20 comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient and maintained in the presence of the chemical or biologic agent, and
- 25 b) expression of the marker in a second sample obtained from the patient and maintained in the absence of the agent.

A significantly lower level of expression of the marker in the first sample relative to that in the second sample is an indication that the agent is efficacious for inhibiting ovarian cancer in the patient. In one embodiment, the first and second samples can be portions of a single sample obtained from the patient or portions of pooled samples obtained
30 from the patient.

The invention additionally provides a monitoring method for assessing the progression of ovarian cancer in a patient, the method comprising:

- a) detecting in a patient sample at a first time point, the expression of a marker of the invention;
- 5 b) repeating step a) at a subsequent time point in time; and
- c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of ovarian cancer in the patient.

A significantly higher level of expression of the marker in the sample at the subsequent time point from that of the sample at the first time point is an indication that the ovarian cancer has progressed, whereas a significantly lower level of expression is an indication
10 that the ovarian cancer has regressed.

The invention further provides a diagnostic method for determining whether ovarian cancer has metastasized or is likely to metastasize in the future, the method comprising comparing:

- 15 a) the level of expression of a marker of the invention in a patient sample, and
- b) the normal level (or non-metastatic level) of expression of the marker in a control sample.

A significantly higher level of expression in the patient sample as compared to the
20 normal level (or non-metastatic level) is an indication that the ovarian cancer has metastasized or is likely to metastasize in the future.

The invention moreover provides a test method for selecting a composition for inhibiting ovarian cancer in a patient. This method comprises the steps of:

- 25 a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- 30 d) selecting one of the test compositions which significantly reduces the level of expression of the marker in the aliquot containing that test

composition, relative to the levels of expression of the marker in the presence of the other test compositions.

The invention additionally provides a test method of assessing the ovarian carcinogenic potential of a compound. This method comprises the steps of:

- 5 a) maintaining separate aliquots of ovarian cells in the presence and absence of the compound; and
- b) comparing expression of a marker of the invention in each of the aliquots.

10 A significantly higher level of expression of the marker in the aliquot maintained in the presence of the compound, relative to that of the aliquot maintained in the absence of the compound, is an indication that the compound possesses ovarian carcinogenic potential.

In addition, the invention further provides a method of inhibiting ovarian cancer in a patient. This method comprises the steps of:

- 15 a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- 20 d) administering to the patient at least one of the compositions which significantly lowers the level of expression of the marker in the aliquot containing that composition, relative to the levels of expression of the marker in the presence of the other compositions.

In the aforementioned methods, the samples or patient samples comprise cells obtained from the patient. The cells may be found in an ovarian tissue sample collected, for example, by an ovarian tissue biopsy or histology section. In one embodiment, the patient sample is an ovary-associated body fluid. Such fluids include, for example, blood fluids, lymph, ascites fluids, gynecological fluids, cystic fluids, urine, and fluids collected by peritoneal rinsing. In another embodiment, the sample comprises cells obtained from the patient. In this embodiment, the cells may be found in

25 a fluid selected from the group consisting of a fluid collected by peritoneal rinsing, a fluid collected by uterine rinsing, a uterine fluid, a uterine exudate, a pleural fluid, and an ovarian exudate. In a further embodiment, the patient sample is *in vivo*.

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According to the invention, the level of expression of a marker of the invention in a sample can be assessed, for example, by detecting the presence in the sample of:

- 5 • the corresponding marker protein or a fragment of the protein (*e.g.* by using a reagent, such as an antibody, an antibody derivative, an antibody fragment or single-chain antibody, which binds specifically with the protein or protein fragment).
- 10 • the corresponding marker nucleic acid or a fragment of the nucleic acid (*e.g.* by contacting transcribed polynucleotides obtained from the sample with a substrate having affixed thereto one or more nucleic acids having the entire or a segment of the sequence or a complement thereof)
- a metabolite which is produced directly (*i.e.*, catalyzed) or indirectly by the corresponding marker protein.

According to the invention, any of the aforementioned methods may be performed using a plurality (*e.g.* 2, 3, 5, or 10 or more) of ovarian cancer markers, including ovarian cancer markers known in the art. In such methods, the level of expression in the sample of each of a plurality of markers, at least one of which is a marker of the invention, is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with ovarian cancer. A significantly altered (*i.e.*, increased or decreased as specified in the above-described methods using a single marker) level of expression in the sample of one or more markers of the invention, or some combination thereof, relative to that marker's corresponding normal levels, is an indication that the patient is afflicted with ovarian cancer. For all of the aforementioned methods, the marker(s) are preferably selected such that the positive predictive value of the method is at least about 10%.

In a further aspect, the invention provides an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein or a fragment of the protein. The invention also provides methods for making such antibody, antibody derivative, and antibody fragment. Such methods may comprise immunizing a mammal with a protein or peptide comprising the entirety, or a segment of 10 amino acids or more, of a marker protein, wherein the protein or peptide may be obtained from

- 11 -

a cell or by chemical synthesis. The methods of the invention also encompass producing monoclonal and single-chain antibodies, which would further comprise isolating splenocytes from the immunized mammal, fusing the isolated splenocytes with an immortalized cell line to form hybridomas, and screening individual hybridomas for those that produce an antibody that binds specifically with a marker protein or a fragment of the protein.

In another aspect, the invention relates to various diagnostic and test kits. In one embodiment, the invention provides a kit for assessing whether a patient is afflicted with ovarian cancer. The kit comprises a reagent for assessing expression of a marker of the invention. In another embodiment, the invention provides a kit for assessing the suitability of a chemical or biologic agent for inhibiting an ovarian cancer in a patient. Such kit comprises a reagent for assessing expression of a marker of the invention, and may also comprise one or more of such agents. In a further embodiment, the invention provides kits for assessing the presence of ovarian cancer cells or treating ovarian cancers. Such kits comprise an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein, or a fragment of the protein. Such kits may also comprise a plurality of antibodies, antibody derivatives, or antibody fragments wherein the plurality of such antibody agents binds specifically with a marker protein, or a fragment of the protein.

In an additional embodiment, the invention also provides a kit for assessing the presence of ovarian cancer cells, wherein the kit comprises a nucleic acid probe that binds specifically with a marker nucleic acid or a fragment of the nucleic acid. The kit may also comprise a plurality of probes, wherein each of the probes binds specifically with a marker nucleic acid, or a fragment of the nucleic acid.

In a further aspect, the invention relates to methods for treating a patient afflicted with ovarian cancer or at risk of developing ovarian cancer. Such methods may comprise reducing the expression and/or interfering with the biological function of a marker of the invention. In one embodiment, the method comprises providing to the patient an antisense oligonucleotide or polynucleotide complementary to a marker nucleic acid, or a segment thereof. For example, an antisense polynucleotide may be provided to the patient through the delivery of a vector that expresses an antisense polynucleotide of a marker nucleic acid or a fragment thereof. In another embodiment,

- 12 -

the method comprises providing to the patient an antibody, an antibody derivative, or antibody fragment, which binds specifically with a marker protein or a fragment of the protein. In a preferred embodiment, the antibody, antibody derivative or antibody fragment binds specifically with a protein having the sequence of any of the markers
5 listed in Table 1, or a fragment of such a protein.

It will be appreciated that the methods and kits of the present invention may also include known cancer markers including known ovarian cancer markers. It will further be appreciated that the methods and kits may be used to identify cancers other than ovarian cancer.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts a graph which represents the results of the TaqMan® expression study.

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DETAILED DESCRIPTION OF THE INVENTION

The invention relates to newly discovered markers, identified in Tables 1-3, that are associated with the cancerous state of ovarian cells. It has been discovered that the higher than normal level of expression of any of these markers or combination of these markers correlates with the presence of ovarian cancer in a patient. Methods
20 are provided for detecting the presence of ovarian cancer in a sample, the absence of ovarian cancer in a sample, the stage of an ovarian cancer, and with other characteristics of ovarian cancer that are relevant to prevention, diagnosis, characterization, and therapy of ovarian cancer in a patient. Methods of treating ovarian cancer are also provided.

Tables 1-3 list the markers of the present invention. In the Tables the
25 markers are identified with a name ("Marker"), the name the gene is commonly known by, if applicable ("Gene Name"), the Sequence Listing identifier of the cDNA sequence of a nucleotide transcript encoded by or corresponding to the marker ("SEQ ID NO (nts)"), the Sequence Listing identifier of the amino acid sequence of a protein encoded by the nucleotide transcript ("SEQ ID NO (AAs)"), and the location of the protein
30 coding sequence within the cDNA sequence ("CDS").

Table 1 lists all of the markers of the invention, which are over-expressed in ovarian cancer cells compared to normal (*i.e.*, non-cancerous) ovarian cells and comprises markers listed in Tables 2 and 3. Table 2 lists newly-identified nucleotide

and amino acid sequences useful as ovarian cancer markers. Table 3 lists newly-identified nucleotide sequences useful as ovarian cancer markers.

In addition to their use in ovarian cancer, it has been found that the markers of the present invention may be used in the diagnosis, characterization, management, and therapy of additional diseases. For example, OV65 (SEQ ID NOS: 305 and 306), M593 (SEQ ID NOS: 307 and 308) and M594 (SEQ ID NOS: 309 and 310), are spondin molecules, and have one or more of the following activities: (1) neural cell adhesion and (2) neurite extension and can thus be used in, for example, the diagnosis and treatment of brain and CNS related disorders. Such brain and CNS related disorders include, but are not limited to, bacterial and viral meningitis, Alzheimers Disease, cerebral toxoplasmosis, Parkinson's disease, multiple sclerosis, brain cancers (*e.g.*, metastatic carcinoma of the brain, glioblastoma, lymphoma, astrocytoma, acoustic neuroma), hydrocephalus, and encephalitis. In another example, OV65, M593 and M594 polypeptides, nucleic acids, and modulators thereof can be used to treat disorders of the brain, such as cerebral edema, hydrocephalus, brain herniations, iatrogenic disease (due to, *e.g.*, infection, toxins, or drugs), inflammations (*e.g.*, bacterial and viral meningitis, encephalitis, and cerebral toxoplasmosis), cerebrovascular diseases (*e.g.*, hypoxia, ischemia, infarction, intracranial hemorrhage, vascular malformations, and hypertensive encephalopathy), and tumors (*e.g.*, neuroglial tumors, neuronal tumors, tumors of pineal cells, meningeal tumors, primary and secondary lymphomas, intracranial tumors, and medulloblastoma), and to treat injury or trauma to the brain.

OV25 (SEQ ID NOS: 360 and 361), an HE4 protein, has one or more of the following activities: (1) sperm maturation and (2) inhibition of extracellular proteases and can thus be used in, for example, the treatment and diagnosis of diseases and disorders relating to spermatogenesis. For example, OV25 polypeptides, nucleic acids, and modulators thereof can be used to treat testicular disorders, such as unilateral testicular enlargement (*e.g.*, nontuberculous, granulomatous orchitis); inflammatory diseases resulting in testicular dysfunction (*e.g.*, gonorrhea and mumps); cryptorchidism; sperm cell disorders (*e.g.*, immotile cilia syndrome and germinal cell aplasia); acquired testicular defects (*e.g.*, viral orchitis); and tumors (*e.g.*, germ cell tumors, interstitial cell tumors, androblastoma, testicular lymphoma and adenomatoid tumors).

OV52 (SEQ ID NOS: 190 and 191), a Pump-1 proteinase, has been found to have one or more of the following activities: (1) breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and remodeling, as well as in (2) disease processes, such as arthritis, and metastasis. Hence, 5 OV52 nucleic acids, proteins, and modulators thereof can be used to modulate disorders associated with adhesion and migration of cells, *e.g.*, platelet aggregation disorders (*e.g.*, Glanzmann's thromboasthenia, which is a bleeding disorder characterized by failure of platelet aggregation in response to cell stimuli), inflammatory disorders (*e.g.*, leukocyte adhesion deficiency, which is a disorder associated with impaired migration of 10 neutrophils to sites of extravascular inflammation), connective tissue disorders, arthritis, disorders associated with abnormal tissue migration during embryo development, and tumor metastasis.

M604 (SEQ ID NOS: 48 and 49), OV10 (SEQ ID NOS: 50 and 51), and M360 (SEQ ID NOS: 52 and 53), are Claudin molecules which have one or more of the 15 following activities: (1) it elicits fluid accumulation in the intestinal tract by altering the membrane permeability of intestinal epithelial cells and (2) thus acts as the causative agent of diarrhea. The polypeptides, nucleic acids, and modulators thereof can be used to treat colonic disorders, such as congenital anomalies (*e.g.*, megacolon and imperforate anus), idiopathic disorders (*e.g.*, diverticular disease and melanosis coli), vascular 20 lesions (*e.g.*, ischemic colitis, hemorrhoids, angiodysplasia), inflammatory diseases (*e.g.*, colitis (*e.g.*, idiopathic ulcerative colitis, pseudomembranous colitis), and lymphopathia venereum), Crohn's disease, and tumors (*e.g.*, hyperplastic polyps, adenomatous polyps, bronchogenic cancer, colonic carcinoma, squamous cell carcinoma, adenoacanthomas, sarcomas, lymphomas, argentaffinomas, carcinoids, and 25 melanocarcinomas).

OV48 (SEQ ID NOS: 226 and 227), OV49 (SEQ ID NOS: 228 and 229) and OV50 (SEQ ID NOS: 230 and 231), markers for an osteopontin protein, have one or more of the following activities: (1) they act as a vessel extracellular matrix protein involved in calcification and (2) atherosclerosis. Hence, OV48, OV49 and OV50 30 nucleic acids, proteins, and modulators thereof can be used to treat heart disorders, *e.g.*, ischemic heart disease, atherosclerosis, hypertension, angina pectoris, Hypertrophic Cardiomyopathy, and congenital heart disease. They can also be used to treat

cardiovascular disorders, such as ischemic heart disease (*e.g.*, angina pectoris, myocardial infarction, and chronic ischemic heart disease), hypertensive heart disease, pulmonary heart disease, valvular heart disease (*e.g.*, rheumatic fever and rheumatic heart disease, endocarditis, mitral valve prolapse, and aortic valve stenosis), congenital
5 heart disease (*e.g.*, valvular and vascular obstructive lesions, atrial or ventricular septal defect, and patent ductus arteriosus), or myocardial disease (*e.g.*, myocarditis, congestive cardiomyopathy, and hypertrophic cardiomyopathy).

OV37 (SEQ ID NOS: 176 and 177), a lipocalin marker, is known to be a component of the neutrophil gelatinase complex. OV37 nucleic acids, proteins, and
10 modulators thereof can be used to modulate the proliferation, differentiation, and/or function of leukocytes. Thus, OV37 nucleic acids, proteins, and modulators thereof can be used to treat bone marrow, blood, and hematopoietic associated diseases and disorders, *e.g.*, acute myeloid leukemia, hemophilia, leukemia, anemia (*e.g.*, sickle cell anemia), and thalassemia. OV37 polypeptides, nucleic acids, and modulators thereof can
15 be used to treat leukocytic disorders, such as leukopenias (*e.g.*, neutropenia, monocytopenia, lymphopenia, and granulocytopenia), leukocytosis (*e.g.*, granulocytosis, lymphocytosis, eosinophilia, monocytosis, acute and chronic lymphadenitis), malignant lymphomas (*e.g.*, Non-Hodgkin's lymphomas, Hodgkin's lymphomas, leukemias, agnogenic myeloid metaplasia, multiple myeloma, plasmacytoma, Waldenstrom's
20 macroglobulinemia, heavy-chain disease, monoclonal gammopathy, histiocytoses, eosinophilic granuloma, and angioimmunoblastic lymphadenopathy).

OV2 (SEQ ID NOS: 285 and 286), is known to be a protease inhibitor, which is associated with emphysema and liver disease. Hence OV2 polypeptides, nucleic acids, and modulators thereof can be used to diagnose and treat pulmonary
25 (lung) disorders, such as atelectasis, cystic fibrosis, rheumatoid lung disease, pulmonary congestion or edema, chronic obstructive airway disease (*e.g.*, emphysema, chronic bronchitis, bronchial asthma, and bronchiectasis), diffuse interstitial diseases (*e.g.*, sarcoidosis, pneumoconiosis, hypersensitivity pneumonitis, bronchiolitis, Goodpasture's syndrome, idiopathic pulmonary fibrosis, idiopathic pulmonary hemosiderosis,
30 pulmonary alveolar proteinosis, desquamative interstitial pneumonitis, chronic interstitial pneumonia, fibrosing alveolitis, hamman-rich syndrome, pulmonary eosinophilia, diffuse interstitial fibrosis, Wegener's granulomatosis, lymphomatoid

granulomatosis, and lipid pneumonia), or tumors (*e.g.*, bronchogenic carcinoma, bronchioloalveolar carcinoma, bronchial carcinoid, hamartoma, and mesenchymal tumors). In another example, OV2 polypeptides, nucleic acids, and modulators thereof can be used to diagnose and treat hepatic (liver) disorders, such as jaundice, hepatic failure, hereditary hyperbilirubinemias (*e.g.*, Gilbert's syndrome, Crigler-Najjar syndromes and Dubin-Johnson and Rotor's syndromes), hepatic circulatory disorders (*e.g.*, hepatic vein thrombosis and portal vein obstruction and thrombosis), hepatitis (*e.g.*, chronic active hepatitis, acute viral hepatitis, and toxic and drug-induced hepatitis), cirrhosis (*e.g.*, alcoholic cirrhosis, biliary cirrhosis, and hemochromatosis), or malignant tumors (*e.g.*, primary carcinoma, hepatoma, hepatoblastoma, liver cysts, and angiosarcoma).

OV32 (SEQ ID NOS: 166 and 167) and OV33 (SEQ ID NOS: 168 and 169), kallikrein markers, are useful in detection of primary mammary carcinomas, as well as primary ovarian cancers. Hence, OV32 and OV33 polypeptides, nucleic acids, and modulators thereof can be used to diagnose and treat ovarian disorders, such as ovarian endometriosis, non-neoplastic cysts (*e.g.*, follicular and luteal cysts and polycystic ovaries) and tumors (*e.g.*, carcinomas, tumors of surface epithelium, germ cell tumors, ovarian fibroma, sex cord-stromal tumors, and ovarian cancers (*e.g.*, metastatic carcinomas, and ovarian teratoma)).

OV68 (SEQ ID NOS: 192 and 193), OV69 (SEQ ID NOS: 194 and 195), OV70 (SEQ ID NOS: 196 and 197), OV71 (SEQ ID NOS: 198 and 199), OV72 (SEQ ID NOS: 200 and 201), OV41 (SEQ ID NOS: 202 and 203), OV42 (SEQ ID NOS: 204 and 205), OV43 (SEQ ID NOS: 206 and 205), OV44 (SEQ ID NOS: 207 and 208) and OV83 (SEQ ID NOS: 209 and 210), are all mesothelin markers, and have been found to play a role in cellular adhesion. The nucleic acids, proteins, and modulators thereof can be used to diagnose, treat and modulate disorders associated with adhesion and migration of cells, *e.g.*, platelet aggregation disorders (*e.g.*, Glanzmann's thrombasthenia, which is a bleeding disorder characterized by failure of platelet aggregation in response to cell stimuli), inflammatory disorders (*e.g.*, leukocyte adhesion deficiency, which is a disorder associated with impaired migration of neutrophils to sites of extravascular inflammation), disorders associated with abnormal tissue migration during embryo development, and tumor metastasis.

- 17 -

OV17 (SEQ ID NOS: 110 and 111), OV18 (SEQ ID NOS: 112 and 111), OV19 (SEQ ID NOS: 113 and 111), OV20 (SEQ ID NOS: 114 and 111), OV21 (SEQ ID NOS: 115 and 111) and OV22 (SEQ ID NOS: 116 and 117) are folate receptors, which are known to be markers of ovarian cancer. The nucleic acids, proteins, and modulators thereof can be used to diagnose, treat and modulate ovarian disorders (*e.g.*, ovarian cyst, ovarian fibroma, ovarian endometriosis, ovarian teratoma). Although these markers have been previously associated with ovarian cancer, the expression of such markers has not yet been identified in combination with the expression of other markers including those of the present invention. Such combination of markers will provide improved methods of diagnosing, characterizing, managing and treating ovarian cancer.

OV66 (SEQ ID NOS: 54 and 55), OV7 (SEQ ID NOS: 56 and 57), OV8 (SEQ ID NOS: 58 and 59) and OV81 (SEQ ID NOS: 60 and 61) are ceruloplasmin markers, known to encode a plasma metalloprotein that binds copper in the plasma. The nucleic acids, proteins, and modulators thereof can be used to diagnose, treat and modulate disorders in blood haemostasis and diseases caused by such an imbalance *e.g.*, (1) cardiovascular diseases or disorders, such as ischemic heart disease (*e.g.*, angina pectoris, myocardial infarction, and chronic ischemic heart disease), hypertensive heart disease, pulmonary heart disease, valvular heart disease (*e.g.*, rheumatic fever and rheumatic heart disease, endocarditis, mitral valve prolapse, and aortic valve stenosis), congenital heart disease (*e.g.*, valvular and vascular obstructive lesions, atrial or ventricular septal defect, and patent ductus arteriosus), or myocardial disease (*e.g.*, myocarditis, congestive cardiomyopathy, and hypertrophic cardiomyopathy); (2) neuronal diseases such as Alzheimers Disease, cerebral toxoplasmosis, Parkinson's disease, multiple sclerosis, brain cancers (*e.g.*, metastatic carcinoma of the brain, glioblastoma, lymphoma, astrocytoma, acoustic neuroma), hydrocephalus, and encephalitis; and (3) Wilson's Disease.

TABLE 1

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
OV1	ABCB1: ATP-binding cassette, sub-family B (MDR/TAP), member 1	1	2	425..4264
M430	ADPRT: ADP-ribosyltransferase	3	4	160..3204
M571	ANXA2: annexin A2, variant 1	5	6	134..1153
M572	ANXA2: annexin A2, variant 2	7	8	50..1069
M573	ANXA4: annexin A4	9	10	74..1039
OV3	AQP5: aquaporin 5	11	12	519..1316
M352	ARHGAP8: Rho GTPase activating protein 8, variant 1	13	14	142..1536
M353	ARHGAP8: Rho GTPase activating protein 8, variant 2	15	16	1..2043
M354	ARHGAP8: Rho GTPase activating protein 8, variant 3	17	18	1..2256
M608	ARHGAP8: Rho GTPase activating protein 8, variant 4	17	19	1..2157
M355	ARHGAP8: Rho GTPase activating protein 8, variant 5	20	21	<1..1314
M356	ARHGAP8: Rho GTPase activating protein 8, variant 6	22	23	1..1902
M357	ARHGAP8: Rho GTPase activating protein 8, variant 7	24	25	<1..1281
M358	ARHGAP8: Rho GTPase activating protein 8, variant 8	26	27	1..1386
M359	ARHGAP8: Rho GTPase activating protein 8, variant 9	28	29	<1..1059
OV5	BICD1: Bicaudal D homolog 1 (Drosophila)	30	31	82..3009
M431	BTG2: BTG family, member 2	32	33	72..548
M432	CADPS: Ca ²⁺ -dependent activator protein for secretion	34	35	240..4412
M609	CDH1: cadherin 1, type 1, E-cadherin (epithelial)	36	37	125..2773
M433	CDH6: cadherin 6, type 2, K-cadherin	38	39	327..2699
M434	CDKN2A: cyclin-dependent kinase inhibitor 2A	40	41	41..511
OV9	CGN: cingulin	42	43	152..3763
OV6	CHI3L1: cartilage glycoprotein-39	44	45	127..1278
M435	CKMT1: creatine kinase, mitochondrial 1 (ubiquitous)	46	47	164..1417
M604	CLDN10: claudin 10	48	49	36..772
OV10	CLDN16: claudin 16	50	51	69..986
M360	CLDN4: claudin 4	52	53	183..812
OV66	CP: ceruloplasmin (ferroxidase), variant 1	54	55	1..3210
OV7	CP: ceruloplasmin (ferroxidase), variant 2	56	57	<1..2561
OV8	CP: ceruloplasmin (ferroxidase), variant 3	58	59	1..3198
OV81	CP: ceruloplasmin (ferroxidase), variant 4	60	61	76..3348
M103	CRABP2: cellular retinoic acid-binding protein 2	62	63	138..554

OV40	DD96: Epithelial protein up-regulated in carcinoma, membrane associated protein 17	64	65	202..546
OV4	DEC2: basic helix-loop-helix protein	66	67	135..1583
M575	dehydrogenase	68	69	339..1364
M436	DLX5: distal-less homeo box 5	70	71	204..1073
OV12	EAB1: Eab1 protein	72	73	<1..1305
OV13	ESX protein	74	75	96..1211
OV67	EVI-1: Evi-1 protein, variant 1	76	77	250..2406
OV14	EVI-1: Evi-1 protein, variant 2	78	79	250..3405
OV15	EVI-1: Evi-1 protein, variant 3	80	81	250..2433
OV16	EVI-1: Evi-1 protein, variant 4	82	83	250..3378
M437	FLJ10546: hypothetical protein FLJ10546	84	85	28..1815
OV28	FLJ12799: hypothetical protein FLJ12799	86	87	39..797
M576	FLJ13710: hypothetical protein FLJ13710	88	89	96..1712
M438	FLJ13782: hypothetical protein FLJ13782	90	91	13..1890
OV29	FLJ20150: hypothetical protein FLJ20150	92	93	78..983
M439	FLJ20327: hypothetical protein FLJ20327	94	95	306..2186
M440	FLJ20758: hypothetical protein FLJ20758, variant 1	96	97	<2..1270
M441	FLJ20758: hypothetical protein FLJ20758, variant 2	98	99	<2..2095
M442	FLJ20758: hypothetical protein FLJ20758, variant 3	100	101	465..1307
M443	FLJ22252: likely ortholog of mouse SRY-box containing gene 17	102	103	205..1449
M444	FLJ22316: hypothetical protein FLJ22316	104	105	508..1206
M400	FLJ22418: hypothetical protein FLJ22418	106	107	71..919
M445	FLJ23499: hypothetical protein FLJ23499	108	109	21..473
OV17	FOLR1: folate receptor 1 (alpha), variant 1	110	111	139..912
OV18	FOLR1: folate receptor 1 (alpha), variant 2	112	111	211..984
OV19	FOLR1: folate receptor 1 (alpha), variant 3	113	111	46..819
OV20	FOLR1: folate receptor 1 (alpha), variant 4	114	111	437..1210
OV21	FOLR1: folate receptor 1 (alpha), variant 5	115	111	11..784
OV22	FOLR3: folate receptor 3 (gamma)	116	117	57..788
OV23	GPR39: G protein-coupled receptor 39	118	119	1..1362
M446	GPRC5B: G protein-coupled receptor, family C, group 5, member B	120	121	109..1320
OV24	G-protein coupled receptor	122	123	274..1236
M447	GRB7: growth factor receptor-bound protein 7	124	125	220..1818
OV11	HAIK1: type I intermediate filament cyto keratin	126	127	61..1329
M448	HOXB7: homeo box B7	128	129	100..753
M138	HSECP1: secretory protein, variant 1	130	131	27..863
M449	HSECP1: secretory protein, variant 2	132	133	136..768
M450	HSECP1: secretory protein, variant 3	134	135	202..933
M451	HSNFRK: HSNFRK protein	136	137	642..2939
OV26	hypothetical protein (1)	138	139	<1..1140
OV27	hypothetical protein (2)	140	141	242..1483
OV31	IFI30: interferon, gamma-inducible protein 30	142	143	41..952
OV58	IGF2: somatomedin A	144	145	553..1095

M452	IMP-2: IGF-II mRNA-binding protein 2	146	147	436..2106
M453	INDO: indoleamine-pyrrole 2, 3 dioxygenase	148	149	23..1234
OV73	IPT: tRNA isopentenylpyrophosphate transferase, variant 1	150	151	15..1418
M610	IPT: tRNA isopentenylpyrophosphate transferase, variant 2	152	153	15..1418
M454	ITGA3: integrin, alpha 3	154	155	74..3274
OV30	ITGB8: integrin, beta 8	156	157	681..2990
OV34	KIAA0762: KIAA0762 protein	158	159	<1..1875
M455	KIAA0869: KIAA0869 protein	160	161	<1..2668
OV35	KIAA1154: KIAA1154 protein	162	163	<1..677
OV36	KIAA1456: KIAA1456 protein	164	165	<366..1631
OV32	KLK10: kallikrein 10	166	167	82..912
OV33	KLK6: kallikrein 6	168	169	246..980
M456	KRT7: keratin 7, variant 1	170	171	57..1466
M611	KRT7: keratin 7, variant 2	172	173	54..1463
OV53	LC27: Putative integral membrane transporter	174	175	204..1055
OV37	LCN2: Lipocalin 2 (oncogene 24p3)	176	177	1..597
M457	LEFTB: left-right determination, factor B	178	179	71..1171
M559	LPHB: lipophilin B (uterglobin family member), prostatein-like	180	181	64..336
OV38	LYST-interacting protein LIP6	182	183	11..586
OV39	MEIS1: MEIS1 protein	184	185	66..1238
M458	MGB2: mammaglobin 2	186	187	65..352
M459	MGC3184: similar to sialyltransferase 7 ((alpha-N-acetylneuraminy 2, 3-betagalactosyl-1, 3)-N-acetyl galactosaminide alpha-2, 6-sialyltransferase) E	188	189	176..1186
OV52	MMP7: Matrix metalloproteinase 7 (matrilysin, uterine)	190	191	28..831
OV68	MSLN: mesothelin, variant 1	192	193	88..2196
OV69	MSLN: mesothelin, variant 2	194	195	88..1980
OV70	MSLN: mesothelin, variant 3	196	197	88..1950
OV71	MSLN: mesothelin, variant 4	198	199	88..2172
OV72	MSLN: mesothelin, variant 5	200	201	88..1926
OV41	MSLN: mesothelin, variant 6	202	203	<1..>1195
OV42	MSLN: mesothelin, variant 7	204	205	85..1953
OV43	MSLN: mesothelin, variant 8	206	205	88..1956
OV44	MSLN: mesothelin, variant 9	207	208	89..1975
OV83	MSLN: mesothelin, variant 10	209	210	295..2187
OV45	MUC1: mucin 1	211	212	58..1605
M460	MUC16: mucin 16, variant 1	213	214	<1..5352
M461	MUC16: mucin 16, variant 2	215	216	25..3471
M612	MUC16: mucin 16, variant 3	215	217	<1..5673
M462	MYOM2: myomesin (M-protein)	218	219	49..4446
M463	NaPi-lib: sodium dependent phosphate transporter isoform	220	221	36..2105
M464	NME5: protein expressed in non-metastatic cells 5	222	223	15..653

OV47	NUFIP1: nuclear fragile X mental retardation protein interacting protein 1	224	225	1..1488
OV48	OPN-a: Secreted phosphoprotein-1 (osteopontin, bone sialoprotein)	226	227	1..942
OV49	OPN-b: Secreted phosphoprotein-1 (osteopontin, bone sialoprotein)	228	229	88..990
OV50	OPN-c: Secreted phosphoprotein-1 (osteopontin, bone sialoprotein)	230	231	1..861
M578	PAEP: progesterone-associated endometrial protein, variant 1	232	233	36..578
M579	PAEP: progesterone-associated endometrial protein, variant 2	234	233	36..578
M580	PAEP: progesterone-associated endometrial protein, variant 3	235	233	36..578
M581	PAEP: progesterone-associated endometrial protein, variant 4	236	233	36..578
M583	PAEP: progesterone-associated endometrial protein, variant 5	237	238	45..305
M582	PAEP: progesterone-associated endometrial protein, variant 6	239	240	45..521
M613	PAEP: progesterone-associated endometrial protein, variant 7	239	241	45..521
M465	PAX8: paired box gene 8, isoform 8A	242	243	11..1363
M466	PAX8: paired box gene 8, isoform 8B, variant 1	244	245	11..1174
M614	PAX8: paired box gene 8, isoform 8B, variant 2	244	246	11..1174
M467	PAX8: paired box gene 8, isoform 8C	247	248	161..1357
M468	PAX8: paired box gene 8, isoform 8D	249	250	161..1126
M469	PAX8: paired box gene 8, isoform 8E	251	252	161..1024
M470	PRAME: preferentially expressed antigen in melanoma	253	254	236..1765
M615	PRKCI: protein kinase C, iota	255	256	205..1968
M605	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 1	257	258	<1..3133
M606	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 2	259	258	<1..3133
M607	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 3	260	258	<1..3133
OV80	PRSS8: prostatic	261	262	229..1260
OV51	PTGS1: prostaglandin-endoperoxide synthase 1	263	264	6..1805
M312	PTK9: protein tyrosine kinase 9	265	266	61..1113
OV54	pyruvate dehydrogenase complex component E2	267	268	49..>358
OV55	S100A1: S100 calcium-binding protein A1	269	270	114..398
M471	S100A11: S100 calcium-binding protein A11 (calgizzarin)	271	272	121..438
M68	S100A2: S100 calcium-binding protein A2	273	274	41..334
M585	S100A6: S100 calcium-binding protein A6 (calcyclin)	275	276	103..375

- 22 -

OV57	SCNN1A: sodium channel, nonvoltage-gated 1 alpha, variant 1	277	278	100..2109
OV85	SCNN1A: sodium channel, nonvoltage-gated 1 alpha, variant 2	279	280	96..2105
M472	secreted protein (HETKL27)	281	282	88..618
M473	SEMA3A: sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A	283	284	16..2331
OV2	SERPINA1: alpha-1 antitrypsin	285	286	35..1291
M474	Similar to hypothetical protein, MGC: 7199	287	288	173..1053
M586	Similar to proteasome (prosome, macropain) subunit, alpha type, 3	289	290	45..791
M587	Similar to zinc finger protein 136	291	292	139..1524
M475	SLPI: secretory leukocyte protease inhibitor (antileukoproteinase), variant 1	293	294	271..447
M185	SLPI: secretory leukocyte protease inhibitor (antileukoproteinase), variant 2	295	296	19..417
OV60	SNCG: synuclein, gamma	297	298	49..432
OV59	SORL1: sortilin-related receptor	299	300	198..6842
OV56	SPINT2: serine protease inhibitor, Kunitz type, 2, variant 1	301	302	301..1059
OV84	SPINT2: serine protease inhibitor, Kunitz type, 2, variant 2	303	304	332..919
OV65	SPON1: VSGP/F-spondin, variant 1	305	306	25..2448
M593	SPON1: VSGP/F-spondin, variant 2	307	308	180..2984
M594	SPON1: VSGP/F-spondin, variant 3	309	310	180..2687
OV82	ST14: matriptase	311	312	209..2557
M476	TACSTD2: tumor-associated calcium signal transducer 2	313	314	616..1587
M588	TFPI2: tissue factor pathway inhibitor 2	315	316	57..764
OV86	TMPRSS4: transmembrane protease, serine 4	317	318	310..1623
OV74	TPH: tryptophan hydroxylase, variant 1	319	320	1..1335
OV75	TPH: tryptophan hydroxylase, variant 2	321	322	1..1401
M327	TSPAN-1: Tetraspan NET-1 protein, variant 1	323	324	124..900
M328	TSPAN-1: Tetraspan NET-1 protein, variant 2	325	326	1..726
OV46	TTID: myotilin	327	328	281..1777
M589	UCH2: Ubiquitin carboxyl-terminal hydrolases family 2	329	330	551..2940
OV63	unnamed gene (1)	331	332	71..919
OV64	unnamed gene (2)	333	334	28..804
OV76	unnamed gene (3)	335	336	69..773
OV77	unnamed gene (4)	337	338	223..1284
OV78	unnamed gene (5), variant 1	339	340	84..2450
M616	unnamed gene (5), variant 2	341	342	84..2450
OV79	unnamed gene (6)	343	344	69..392
OV87	unnamed gene (7)	345	346	509..2428
OV88	unnamed gene (8)	347	348	71..919
M477	unnamed gene (9), variant 1	349	350	246..992
M617	unnamed gene (9), variant 2	349	351	246..992
M478	unnamed gene (9), variant 3	352	353	246..1004

- 23 -

M479	unnamed gene (9), variant 4	354	355	246..1049
M590	unnamed gene (10), variant 1	356	357	21..404
M591	unnamed gene (10), variant 2	358	357	21..404
M592	unnamed gene (10), variant 3	359	357	21..404
OV25	WFDC2: Epididymis-specific, whey-acidic protein type, four-disulfide core; putative ovarian carcinoma marker	360	361	28..405
M480	XRCC5, KU80: ATP-dependant DNA helicase II	362	363	34..2232

TABLE 2

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M354	ARHGAP8: Rho GTPase activating protein 8, variant 3	17	18	1..2256
M608	ARHGAP8: Rho GTPase activating protein 8, variant 4	17	19	1..2157
M355	ARHGAP8: Rho GTPase activating protein 8, variant 5	20	21	<1..1314
M356	ARHGAP8: Rho GTPase activating protein 8, variant 6	22	23	1..1902
M357	ARHGAP8: Rho GTPase activating protein 8, variant 7	24	25	<1..1281
M358	ARHGAP8: Rho GTPase activating protein 8, variant 8	26	27	1..1386
M359	ARHGAP8: Rho GTPase activating protein 8, variant 9	28	29	<1..1059
OV66	CP: ceruloplasmin (ferroxidase), variant 1	54	55	1..3210
OV81	CP: ceruloplasmin (ferroxidase), variant 4	60	61	76..3348
M575	dehydrogenase	68	69	339..1364
OV67	EVI-1: Evi-1 protein, variant 1	76	77	250..2406
M440	FLJ20758: hypothetical protein FLJ20758, variant 1	96	97	<2..1270
M441	FLJ20758: hypothetical protein FLJ20758, variant 2	98	99	<2..2095
M449	HSECP1: secretory protein, variant 2	132	133	136..768
M450	HSECP1: secretory protein, variant 3	134	135	202..933
OV73	IPT: tRNA isopentenylpyrophosphate transferase, variant 1	150	151	15..1418
M610	IPT: tRNA isopentenylpyrophosphate transferase, variant 2	152	153	15..1418
M611	KRT7: keratin 7, variant 2	172	173	54..1463
OV68	MSLN: mesothelin, variant 1	192	193	88..2196
OV69	MSLN: mesothelin, variant 2	194	195	88..1980
OV70	MSLN: mesothelin, variant 3	196	197	88..1950
OV71	MSLN: mesothelin, variant 4	198	199	88..2172
OV72	MSLN: mesothelin, variant 5	200	201	88..1926
OV83	MSLN: mesothelin, variant 10	209	210	295..2187
M460	MUC16: mucin 16, variant 1	213	214	<1..5352
M583	PAEP: progesterone-associated endometrial protein, variant 5	237	238	45..305

- 24 -

M613	PAEP: progesterone-associated endometrial protein, variant 7	239	241	45..521
M614	PAX8: paired box gene 8, isoform 8B, variant 2	244	246	11..1174
M605	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 1	257	258	<1..3133
M606	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 2	259	258	<1..3133
M607	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 3	260	258	<1..3133
OV85	SCNN1A: sodium channel, nonvoltage-gated 1 alpha, variant 2	279	280	96..2105
M475	SLPI: secretory leukocyte protease inhibitor (antileukoproteinase), variant 1	293	294	271..447
OV84	SPINT2: serine protease inhibitor, Kunitz type, 2, variant 2	303	304	332..919
M593	SPON1: VSGP/F-spondin, variant 2	307	308	180..2984
M594	SPON1: VSGP/F-spondin, variant 3	309	310	180..2687
OV82	ST14: matriptase	311	312	209..2557
OV86	TMPRSS4: transmembrane protease, serine 4	317	318	310..1623
OV74	TPH: tryptophan hydroxylase, variant 1	319	320	1..1335
OV75	TPH: tryptophan hydroxylase, variant 2	321	322	1..1401
M327	TSPAN-1: Tetraspan NET-1 protein, variant 1	323	324	124..900
M589	UCH2: Ubiquitin carboxyl-terminal hydrolases family 2	329	330	551..2940
OV76	unnamed gene (3)	335	336	69..773
OV77	unnamed gene (4)	337	338	223..1284
OV78	unnamed gene (5), variant 1	339	340	84..2450
M616	unnamed gene (5), variant 2	341	342	84..2450
OV79	unnamed gene (6)	343	344	69..392
OV87	unnamed gene (7)	345	346	509..2428
OV88	unnamed gene (8)	347	348	71..919
M477	unnamed gene (9), variant 1	349	350	246..992
M617	unnamed gene (9), variant 2	349	351	246..992
M478	unnamed gene (9), variant 3	352	353	246..1004
M479	unnamed gene (9), variant 4	354	355	246..1049

TABLE 3

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M604	CLDN10: claudin 10	48	49	36..772
OV14	EVI-1: Evi-1 protein, variant 2	78	79	250..3405
OV15	EVI-1: Evi-1 protein, variant 3	80	81	250..2433
OV16	EVI-1: Evi-1 protein, variant 4	82	83	250..3378
M576	FLJ13710: hypothetical protein FLJ13710	88	89	96..1712
M444	FLJ22316: hypothetical protein FLJ22316	104	105	508..1206
OV30	ITGB8: integrin, beta 8	156	157	681..2990
OV43	MSLN: mesothelin, variant 8	206	205	88..1956

M581	PAEP: progestagen-associated endometrial protein, variant 4	236	233	36..578
M582	PAEP: progestagen-associated endometrial protein, variant 6	239	240	45..521
M466	PAX8: paired box gene 8, isoform 8B, variant 1	244	245	11..1174
M467	PAX8: paired box gene 8, isoform 8C	247	248	161..1357
M468	PAX8: paired box gene 8, isoform 8D	249	250	161..1126
M469	PAX8: paired box gene 8, isoform 8E	251	252	161..1024
OV2	SERPINA1: alpha-1 antitrypsin	285	286	35..1291
M474	Similar to hypothetical protein, MGC: 7199	287	288	173..1053
M590	unnamed gene (10), variant 1	356	357	21..404
M591	unnamed gene (10), variant 2	358	357	21..404
M592	unnamed gene (10), variant 3	359	357	21..404

Definitions

As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

A "marker" is a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as cancer. A "marker nucleic acid" is a nucleic acid (*e.g.*, mRNA, cDNA) encoded by or corresponding to a marker of the invention. Such marker nucleic acids can be DNA (*e.g.*, cDNA) comprising the sequences listed in Table 1 or the complement of such sequences. The marker nucleic acids also can be RNA comprising the sequences listed in Table 1 or the complement of such sequence, wherein all thymidine residues are replaced with uridine residues. A "marker protein" is a protein encoded by or corresponding to a marker of the invention. A marker protein comprises the sequence of any of the sequences listed in Table 1. The terms "protein" and "polypeptide" are used interchangeably.

The term "probe" refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example, a nucleotide transcript or protein encoded by or corresponding to a marker. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be

labeled, as described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

An "ovary-associated" body fluid is a fluid which, when in the body of a patient, contacts or passes through ovarian cells or into which cells or proteins shed from ovarian cells *e.g.*, ovarian epithelium, are capable of passing. Exemplary ovary-associated body fluids include blood fluids, lymph, ascites, gynecological fluids, cystic fluid, urine, and fluids collected by peritoneal rinsing.

The "normal" level of expression of a marker is the level of expression of the marker in ovarian cells of a human subject or patient not afflicted with ovarian cancer

An "over-expression" or "significantly higher level of expression" of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least twice, and more preferably three, four, five or ten times the expression level of the marker in a control sample (*e.g.*, sample from a healthy subjects not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue-specific manner.

A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

A "tissue-specific" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

5 A "transcribed polynucleotide" or "nucleotide transcript" is a polynucleotide (*e.g.* an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or homologous with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (*e.g.* splicing), if any, of the RNA transcript, and reverse transcription of the
10 RNA transcript.

"Complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of
15 a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the
20 two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at
25 least about 95% of the nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

"Homologous" as used herein, refers to nucleotide sequence similarity
30 between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first

region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

A molecule is "fixed" or "affixed" to a substrate if it is covalently or non-covalently associated with the substrate such the substrate can be rinsed with a fluid (*e.g.* standard saline citrate, pH 7.4) without a substantial fraction of the molecule dissociating from the substrate.

As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in an organism found in nature.

A cancer is "inhibited" if at least one symptom of the cancer is alleviated, terminated, slowed, or prevented. As used herein, ovarian cancer is also "inhibited" if recurrence or metastasis of the cancer is reduced, slowed, delayed, or prevented.

A kit is any manufacture (*e.g.* a package or container) comprising at least one reagent, *e.g.* a probe, for specifically detecting the expression of a marker of the invention. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention.

"Proteins of the invention" encompass marker proteins and their fragments; variant marker proteins and their fragments; peptides and polypeptides comprising an at least 15 amino acid segment of a marker or variant marker protein; and fusion proteins comprising a marker or variant marker protein, or an at least 15 amino acid segment of a marker or variant marker protein.

- 29 -

Unless otherwise specified herewithin, the terms “antibody” and “antibodies” broadly encompass naturally-occurring forms of antibodies (*e.g.*, IgG, IgA, IgM, IgE) and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies, as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to an antibody moiety.

Description

The present invention is based, in part, on newly identified markers which are over-expressed in ovarian cancer cells as compared to their expression in normal (*i.e.* non-cancerous) ovarian cells. The enhanced expression of one or more of these markers in ovarian cells is herein correlated with the cancerous state of the tissue. The invention provides compositions, kits, and methods for assessing the cancerous state of ovarian cells (*e.g.* cells obtained from a human, cultured human cells, archived or preserved human cells and *in vivo* cells) as well as treating patients afflicted with ovarian cancer.

The compositions, kits, and methods of the invention have the following uses, among others:

- 1) assessing whether a patient is afflicted with ovarian cancer;
- 2) assessing the stage of ovarian cancer in a human patient;
- 3) assessing the grade of ovarian cancer in a patient;
- 4) assessing the benign or malignant nature of ovarian cancer in a patient;
- 5) assessing the metastatic potential of ovarian cancer in a patient;
- 6) assessing the histological type of neoplasm (*e.g.* serous, mucinous, endometroid, or clear cell neoplasm) associated with ovarian cancer in a patient;
- 7) making antibodies, antibody fragments or antibody derivatives that are useful for treating ovarian cancer and/or assessing whether a patient is afflicted with ovarian cancer;

- 30 -

- 8) assessing the presence of ovarian cancer cells;
- 9) assessing the efficacy of one or more test compounds for inhibiting ovarian cancer in a patient;
- 10) assessing the efficacy of a therapy for inhibiting ovarian cancer in a patient;
- 11) monitoring the progression of ovarian cancer in a patient;
- 12) selecting a composition or therapy for inhibiting ovarian cancer in a patient;
- 13) treating a patient afflicted with ovarian cancer;
- 14) inhibiting ovarian cancer in a patient;
- 15) assessing the ovarian carcinogenic potential of a test compound; and
- 16) preventing the onset of ovarian cancer in a patient at risk for developing ovarian cancer.

The invention thus includes a method of assessing whether a patient is afflicted with ovarian cancer which includes assessing whether the patient has pre-metastasized ovarian cancer. This method comprises comparing the level of expression of a marker of the invention (listed in Table 1) in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a non-ovarian cancer sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with ovarian cancer.

Gene delivery vehicles, host cells and compositions (all described herein) containing nucleic acids comprising the entirety, or a segment of 15 or more nucleotides, of any of the sequences listed in Tables 1-3 or the complement of such sequences, and polypeptides comprising the entirety, or a segment of 10 or more amino acids, of any of the sequences listed in Tables 1-3 are also provided by this invention.

As described herein, ovarian cancer in patients is associated with an increased level of expression of one or more markers of the invention. While, as discussed above, some of these changes in expression level result from occurrence of the ovarian cancer, others of these changes induce, maintain, and promote the cancerous state of ovarian cancer cells. Thus, ovarian cancer characterized by an increase in the level of expression of one or more markers of the invention can be inhibited by reducing

- 31 -

and/or interfering with the expression of the markers and/or function of the proteins encoded by those markers.

Expression of a marker of the invention can be inhibited in a number of ways generally known in the art. For example, an antisense oligonucleotide can be provided to the ovarian cancer cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment which specifically binds a marker protein, and operably linked with an appropriate promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein. The expression and/or function of a marker may also be inhibited by treating the ovarian cancer cell with an antibody, antibody derivative or antibody fragment that specifically binds a marker protein. Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit expression of a marker or inhibit the function of a marker protein. The compound so identified can be provided to the patient in order to inhibit ovarian cancer cells of the patient.

Any marker or combination of markers of the invention, as well as any known markers in combination with the markers of the invention, may be used in the compositions, kits, and methods of the present invention. In general, it is preferable to use markers for which the difference between the level of expression of the marker in ovarian cancer cells and the level of expression of the same marker in normal ovarian cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is preferred that the difference be at least greater than the standard error of the assessment method, and preferably a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 100-, 500-, 1000-fold or greater than the level of expression of the same marker in normal ovarian tissue.

It is recognized that certain marker proteins are secreted from ovarian cells (*i.e.* one or both of normal and cancerous cells) to the extracellular space surrounding the cells. These markers are preferably used in certain embodiments of the compositions, kits, and methods of the invention, owing to the fact that the such marker

- 32 -

proteins can be detected in an ovary-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, preferred *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled
5 with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

It is a simple matter for the skilled artisan to determine whether any particular marker protein is a secreted protein. In order to make this determination, the marker protein is expressed in, for example, a mammalian cell, preferably a human
10 ovarian cell line, extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (*e.g.* using a labeled antibody which binds specifically with the protein).

The following is an example of a method which can be used to detect secretion of a protein. About 8×10^5 293T cells are incubated at 37°C in wells
15 containing growth medium (Dulbecco's modified Eagle's medium {DMEM} supplemented with 10% fetal bovine serum) under a 5% (v/v) CO₂, 95% air atmosphere to about 60-70% confluence. The cells are then transfected using a standard transfection mixture comprising 2 micrograms of DNA comprising an expression vector encoding the protein and 10 microliters of LipofectAMINE™ (GIBCO/BRL Catalog no. 18342-
20 012) per well. The transfection mixture is maintained for about 5 hours, and then replaced with fresh growth medium and maintained in an air atmosphere. Each well is gently rinsed twice with DMEM which does not contain methionine or cysteine (DMEM-MC; ICN Catalog no. 16-424- 54). About 1 milliliter of DMEM-MC and about 50 microcuries of Trans-³⁵S™ reagent (ICN Catalog no. 51006) are added to each
25 well. The wells are maintained under the 5% CO₂ atmosphere described above and incubated at 37°C for a selected period. Following incubation, 150 microliters of conditioned medium is removed and centrifuged to remove floating cells and debris. The presence of the protein in the supernatant is an indication that the protein is secreted.

Examples of ovary-associated body fluids include blood fluids (*e.g.* whole blood, blood serum, blood having platelets removed therefrom, etc.), lymph, ascitic fluids, gynecological fluids (*e.g.* ovarian, fallopian, and uterine secretions, menses, vaginal douching fluids, fluids used to rinse ovarian cell samples, etc.), cystic
5 fluid, urine, and fluids collected by peritoneal rinsing (*e.g.* fluids applied and collected during laparoscopy or fluids instilled into and withdrawn from the peritoneal cavity of a human patient). In these embodiments, the level of expression of the marker can be assessed by assessing the amount (*e.g.* absolute amount or concentration) of the marker protein in an ovary-associated body fluid obtained from a patient. The fluid can, of
10 course, be subjected to a variety of well-known post-collection preparative and storage techniques (*e.g.* storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the fluid.

Many ovary-associated body fluids (*i.e.* usually excluding urine) can have ovarian cells, *e.g.* ovarian epithelium, therein, particularly when the ovarian cells
15 are cancerous, and, more particularly, when the ovarian cancer is metastasizing. Cell-containing fluids which can contain ovarian cancer cells include, but are not limited to, peritoneal ascites, fluids collected by peritoneal rinsing, fluids collected by uterine rinsing, uterine fluids such as uterine exudate and menses, pleural fluid, and ovarian exudates. Thus, the compositions, kits, and methods of the invention can be used to
20 detect expression of marker proteins having at least one portion which is displayed on the surface of cells which express it. It is a simple matter for the skilled artisan to determine whether a marker protein, or a portion thereof, is exposed on the cell surface. For example, immunological methods may be used to detect such proteins on whole cells, or well known computer-based sequence analysis methods (*e.g.* the SIGNALP
25 program; Nielsen *et al.*, 1997, *Protein Engineering* 10:1-6) may be used to predict the presence of at least one extracellular domain (*i.e.* including both secreted proteins and proteins having at least one cell-surface domain). Expression of a marker protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (*e.g.* using a labeled antibody which binds
30 specifically with a cell-surface domain of the protein).

Expression of a marker of the invention may be assessed by any of a wide variety of well known methods for detecting expression of a transcribed nucleic acid or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein
5 purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods.

In a preferred embodiment, expression of a marker is assessed using an antibody (*e.g.* a radio-labeled, chromophore-labeled, fluorophore-labeled, or enzyme-
10 labeled antibody), an antibody derivative (*e.g.* an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair {*e.g.* biotin-streptavidin}), or an antibody fragment (*e.g.* a single-chain antibody, an isolated antibody hypervariable domain, etc.) or derivative which binds specifically with a marker protein or fragment thereof, including a marker protein which has undergone all or a portion of its normal
15 post-translational modification.

In another preferred embodiment, expression of a marker is assessed by preparing mRNA/cDNA (*i.e.* a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof. cDNA can, optionally, be
20 amplified using any of a variety of polymerase chain reaction methods prior to hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the many known methods of detecting mutations or variants (*e.g.* single nucleotide polymorphisms,
25 deletions, etc.) of a marker of the invention may be used to detect occurrence of a marker in a patient.

In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (*e.g.* at least 7,
30 10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker nucleic acid. If polynucleotides complementary to or homologous with several marker nucleic acids are differentially detectable on the substrate (*e.g.* detectable using different

chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (*e.g.* a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of assessing marker expression is used which involves hybridization of one nucleic acid with another, it is preferred that the hybridization be performed under stringent hybridization conditions.

Because the compositions, kits, and methods of the invention rely on detection of a difference in expression levels of one or more markers of the invention, it is preferable that the level of expression of the marker is significantly greater than the minimum detection limit of the method used to assess expression in at least one of normal ovarian cells and cancerous ovarian cells.

It is understood that by routine screening of additional patient samples using one or more of the markers of the invention, it will be realized that certain of the markers are over-expressed in cancers of various types, including specific ovarian cancers, as well as other cancers such as breast cancer, cervical cancer, etc. For example, it will be confirmed that some of the markers of the invention are over-expressed in most (*i.e.* 50% or more) or substantially all (*i.e.* 80% or more) of ovarian cancer. Furthermore, it will be confirmed that certain of the markers of the invention are associated with ovarian cancer of various stages (*i.e.* stage I, II, III, and IV ovarian cancers, as well as subclassifications IA, IB, IC, IIA, IIB, IIC, IIIA, IIIB, and IIIC, using the FIGO Stage Grouping system for primary carcinoma of the ovary; 1987, *Am. J. Obstet. Gynecol.* 156:236), of various histologic subtypes (*e.g.* serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal (Müllerian) mixed tumor, mesonephroid tumor, malignant carcinoma, Brenner tumor, mixed epithelial tumor, and undifferentiated carcinoma, using the WHO/FIGO system for classification of malignant ovarian tumors; Scully, *Atlas of Tumor Pathology*, 3d series, Washington DC), and various grades (*i.e.* grade I {well differentiated} , grade II {moderately well differentiated}, and grade III {poorly differentiated from surrounding normal tissue}).

In addition, as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that increased expression of certain of the markers of the invention are strongly correlated with malignant cancers and that increased expression of other markers of the invention are strongly correlated with benign tumors. The compositions, kits, and methods of the invention are thus useful for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of ovarian cancer in patients. In addition, these compositions, kits, and methods can be used to detect and differentiate epithelial, stromal, and germ cell ovarian cancers.

When the compositions, kits, and methods of the invention are used for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of ovarian cancer in a patient, it is preferred that the marker or panel of markers of the invention is selected such that a positive result is obtained in at least about 20%, and preferably at least about 40%, 60%, or 80%, and more preferably in substantially all patients afflicted with an ovarian cancer of the corresponding stage, grade, histological type, or benign/malignant nature. Preferably, the marker or panel of markers of the invention is selected such that a PPV of greater than about 10% is obtained for the general population (more preferably coupled with an assay specificity greater than 99.5%).

When a plurality of markers of the invention are used in the compositions, kits, and methods of the invention, the level of expression of each marker in a patient sample can be compared with the normal level of expression of each of the plurality of markers in non-cancerous samples of the same type, either in a single reaction mixture (*i.e.* using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a significantly increased level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with ovarian cancer. When a plurality of markers is used, it is preferred that 2, 3, 4, 5, 8, 10, 12, 15, 20, 30, or 50 or more individual markers be used, wherein fewer markers are preferred.

In order to maximize the sensitivity of the compositions, kits, and methods of the invention (*i.e.* by interference attributable to cells of non-ovarian origin in a patient sample), it is preferable that the marker of the invention used therein be a marker which has a restricted tissue distribution, *e.g.*, normally not expressed in a non-epithelial tissue, and more preferably a marker which is normally not expressed in a non-ovarian tissue.

Only a small number of markers are known to be associated with ovarian cancers (*e.g.* *AKT2*, *Ki-RAS*, *ERBB2*, *c-MYC*, *RBI*, and *TP53*; Lynch, *supra*). These markers are not, of course, included among the markers of the invention, although they may be used together with one or more markers of the invention in a panel of markers, for example. It is well known that certain types of genes, such as oncogenes, tumor suppressor genes, growth factor-like genes, protease-like genes, and protein kinase-like genes are often involved with development of cancers of various types. Thus, among the markers of the invention, use of those which correspond to proteins which resemble proteins encoded by known oncogenes and tumor suppressor genes, and those which correspond to proteins which resemble growth factors, proteases, and protein kinases are preferred.

It is recognized that the compositions, kits, and methods of the invention will be of particular utility to patients having an enhanced risk of developing ovarian cancer and their medical advisors. Patients recognized as having an enhanced risk of developing ovarian cancer include, for example, patients having a familial history of ovarian cancer, patients identified as having a mutant oncogene (*i.e.* at least one allele), and patients of advancing age (*i.e.* women older than about 50 or 60 years).

The level of expression of a marker in normal (*i.e.* non-cancerous) human ovarian tissue can be assessed in a variety of ways. In one embodiment, this normal level of expression is assessed by assessing the level of expression of the marker in a portion of ovarian cells which appears to be non-cancerous and by comparing this normal level of expression with the level of expression in a portion of the ovarian cells which is suspected of being cancerous. For example, when laparoscopy or other medical procedure, reveals the presence of a lump on one portion of a patient's ovary, but not on another portion of the same ovary or on the other ovary, the normal level of expression of a marker may be assessed using one or both of the non-affected ovary and

a non-affected portion of the affected ovary, and this normal level of expression may be compared with the level of expression of the same marker in an affected portion (*i.e.* the lump) of the affected ovary. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers of the invention may be used. In other embodiments, the 'normal' level of expression of a marker may be determined by assessing expression of the marker in a patient sample obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of ovarian cancer in the patient, from archived patient samples, and the like.

The invention includes compositions, kits, and methods for assessing the presence of ovarian cancer cells in a sample (*e.g.* an archived tissue sample or a sample obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the sample to be used is a paraffinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions of the invention, in the kits of the invention, or the methods used to assess levels of marker expression in the sample. Such methods are well known in the art and within the skill of the ordinary artisan.

The invention includes a kit for assessing the presence of ovarian cancer cells (*e.g.* in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a marker nucleic acid or protein. Suitable reagents for binding with a marker protein include antibodies, antibody derivatives, antibody fragments, and the like. Suitable reagents for binding with a marker nucleic acid (*e.g.* a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

The kit of the invention may optionally comprise additional components useful for performing the methods of the invention. By way of example, the kit may comprise fluids (*e.g.* SSC buffer) suitable for annealing complementary nucleic acids or for binding an antibody with a protein with which it specifically binds, one or more
5 sample compartments, an instructional material which describes performance of a method of the invention, a sample of normal ovarian cells, a sample of ovarian cancer cells, and the like.

The invention also includes a method of making an isolated hybridoma which produces an antibody useful for assessing whether patient is afflicted with an
10 ovarian cancer. In this method, a protein or peptide comprising the entirety or a segment of a marker protein is synthesized or isolated (*e.g.* by purification from a cell in which it is expressed or by transcription and translation of a nucleic acid encoding the protein or peptide *in vivo* or *in vitro* using known methods). A vertebrate, preferably a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the protein or peptide. The
15 vertebrate may optionally (and preferably) be immunized at least one additional time with the protein or peptide, so that the vertebrate exhibits a robust immune response to the protein or peptide. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods well known in the art. Hybridomas formed in this manner are then screened
20 using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the marker protein or a fragment thereof. The invention also includes hybridomas made by this method and antibodies made using such hybridomas.

The invention also includes a method of assessing the efficacy of a test
25 compound for inhibiting ovarian cancer cells. As described above, differences in the level of expression of the markers of the invention correlate with the cancerous state of ovarian cells. Although it is recognized that changes in the levels of expression of certain of the markers of the invention likely result from the cancerous state of ovarian cells, it is likewise recognized that changes in the levels of expression of other of the
30 markers of the invention induce, maintain, and promote the cancerous state of those cells. Thus, compounds which inhibit an ovarian cancer in a patient will cause the level of expression of one or more of the markers of the invention to change to a level nearer

the normal level of expression for that marker (*i.e.* the level of expression for the marker in non-cancerous ovarian cells).

This method thus comprises comparing expression of a marker in a first ovarian cell sample and maintained in the presence of the test compound and expression
5 of the marker in a second ovarian cell sample and maintained in the absence of the test compound. A significantly reduced expression of a marker of the invention in the presence of the test compound is an indication that the test compound inhibits ovarian cancer. The ovarian cell samples may, for example, be aliquots of a single sample of normal ovarian cells obtained from a patient, pooled samples of normal ovarian cells
10 obtained from a patient, cells of a normal ovarian cell line, aliquots of a single sample of ovarian cancer cells obtained from a patient, pooled samples of ovarian cancer cells obtained from a patient, cells of an ovarian cancer cell line, or the like. In one embodiment, the samples are ovarian cancer cells obtained from a patient and a plurality of compounds known to be effective for inhibiting various ovarian cancers are tested in
15 order to identify the compound which is likely to best inhibit the ovarian cancer in the patient.

This method may likewise be used to assess the efficacy of a therapy for inhibiting ovarian cancer in a patient. In this method, the level of expression of one or more markers of the invention in a pair of samples (one subjected to the therapy, the
20 other not subjected to the therapy) is assessed. As with the method of assessing the efficacy of test compounds, if the therapy induces a significantly lower level of expression of a marker of the invention then the therapy is efficacious for inhibiting ovarian cancer. As above, if samples from a selected patient are used in this method, then alternative therapies can be assessed *in vitro* in order to select a therapy most likely
25 to be efficacious for inhibiting ovarian cancer in the patient.

As described above, the cancerous state of human ovarian cells is correlated with changes in the levels of expression of the markers of the invention. The invention includes a method for assessing the human ovarian cell carcinogenic potential of a test compound. This method comprises maintaining separate aliquots of human
30 ovarian cells in the presence and absence of the test compound. Expression of a marker of the invention in each of the aliquots is compared. A significantly higher level of expression of a marker of the invention in the aliquot maintained in the presence of the

test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses human ovarian cell carcinogenic potential. The relative carcinogenic potentials of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

Various aspects of the invention are described in further detail in the following subsections.

10 I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker nucleic acid molecules, *e.g.*, those suitable for use as PCR primers for the amplification or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein-encoding sequences) which naturally flank the nucleic acid (*i.e.*, sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques,

or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook *et al.*, ed., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. The probe comprises a label group attached thereto, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes
5 can be used as part of a diagnostic test kit for identifying cells or tissues which mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

The invention further encompasses nucleic acid molecules that differ, due
10 to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein and thus encode the same protein.

It will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence can exist within a population (*e.g.*, the human population). Such genetic polymorphisms can exist among
15 individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist that may affect the overall expression level of that gene (*e.g.*, by affecting regulation or degradation).

20 As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide corresponding
25 to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid
30 polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

In another embodiment, an isolated nucleic acid molecule of the invention is at least 7, 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent
5 conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found
10 in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C.

In addition to naturally-occurring allelic variants of a nucleic acid
15 molecule of the invention that can exist in the population, the skilled artisan will further appreciate that sequence changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein encoded thereby. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino
20 acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologs of various species may be non-essential for activity and thus would be likely targets for alteration.
25 Alternatively, amino acid residues that are conserved among the homologs of various species (*e.g.*, murine and human) may be essential for activity and thus would not be likely targets for alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a variant marker protein that contain changes in amino acid residues
30 that are not essential for activity. Such variant marker proteins differ in amino acid sequence from the naturally-occurring marker proteins, yet retain biological activity. In one embodiment, such a variant marker protein has an amino acid sequence that is at

- 45 -

least about 40% identical, 50%, 60%, 70%, 80%, 90%, 95%, or 98% identical to the amino acid sequence of a marker protein.

An isolated nucleic acid molecule encoding a variant marker protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of marker nucleic acids, such that one or more amino acid residue substitutions, additions, or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

The present invention encompasses antisense nucleic acid molecules, *i.e.*, molecules which are complementary to a sense nucleic acid of the invention, *e.g.*, complementary to the coding strand of a double-stranded marker cDNA molecule or complementary to a marker mRNA sequence. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (*i.e.* anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can also be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a marker protein.

The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (*v*), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (*v*), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (*acp3*)*w*, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a marker protein to thereby inhibit expression of the marker, *e.g.*, by inhibiting transcription and/or translation. The

hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. Examples of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site or infusion of the antisense nucleic acid into an ovary-associated body fluid. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

An antisense nucleic acid molecule of the invention can be an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual α -units, the strands run parallel to each other (Gaultier *et al.*, 1987, *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-*o*-methylribonucleotide (Inoue *et al.*, 1987, *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes as described in Haselhoff and Gerlach, 1988, *Nature* 334:585-591) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a marker protein can be designed based upon the nucleotide sequence of a cDNA corresponding to the marker. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved

(see Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742). Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, *e.g.*, Bartel and Szostak, 1993, *Science* 261:1411-1418).

5 The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a marker of the invention can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the marker nucleic acid or protein (*e.g.*, the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See
10 generally Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

 In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose
15 phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup *et al.*, 1996, *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a
 pseudopeptide backbone and only the four natural nucleobases are retained. The neutral
20 backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup
et al. (1996), *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:14670-675.

25 PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction
30 enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup (1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, *supra*; Perry-O'Keefe *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:14670-675).

In another embodiment, PNAs can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated
5 which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, *e.g.*, RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and
10 orientation (Hyrup, 1996, *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), *supra*, and Finn *et al.* (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can
15 be used as a link between the PNA and the 5' end of DNA (Mag *et al.*, 1989, *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn *et al.*, 1996, *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser *et al.*, 1975,
20 *Bioorganic Med. Chem. Lett.* 5:1119-11124).

In other embodiments, the oligonucleotide can include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.*, 1987, *Proc. Natl. Acad. Sci. USA*
25 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *Bio/Techniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, *e.g.*, a peptide,
30 hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5,876,930.

II. Isolated Proteins and Antibodies

One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is

also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

Preferred marker proteins are encoded by nucleotide sequences comprising the sequences listed in Tables 1-3. Other useful proteins are substantially identical (*e.g.*, at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences

- 52 -

is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions (*e.g.*, overlapping positions) $\times 100$). In one embodiment the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the BLASTN program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (*e.g.*, BLASTX and BLASTN) can be used. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a *k*-tuple value of 2.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The invention also provides chimeric or fusion proteins comprising a marker protein or a segment thereof. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a marker protein operably linked to a heterologous polypeptide (*i.e.*, a polypeptide other than the marker protein). Within the fusion protein, the term "operably linked" is intended to indicate that the marker protein or segment thereof and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the amino-terminus or the carboxyl-terminus of the marker protein or segment.

One useful fusion protein is a GST fusion protein in which a marker protein or segment is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a marker protein can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook *et al.*, *supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a marker protein is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a

cognate ligand of a marker protein. Inhibition of ligand/receptor interaction can be useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies
5 directed against a marker protein in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of the marker protein with ligands.

Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers.

- 10 Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, *e.g.*, Ausubel *et al.*, *supra*). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide).
15 A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

- A signal sequence can be used to facilitate secretion and isolation of marker proteins. Signal sequences are typically characterized by a core of hydrophobic
20 amino acids which are generally cleaved from the mature protein during secretion in one or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to marker proteins, fusion proteins or segments thereof having a signal sequence, as well as to such proteins from which the
25 signal sequence has been proteolytically cleaved (*i.e.*, the cleavage products). In one embodiment, a nucleic acid sequence encoding a signal sequence can be operably linked in an expression vector to a protein of interest, such as a marker protein or a segment thereof. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is
30 subsequently or concurrently cleaved. The protein can then be readily purified from the extracellular medium by art recognized methods. Alternatively, the signal sequence can

be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

The present invention also pertains to variants of the marker proteins. Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function. Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

Variants of a marker protein which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the marker proteins from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, 1983, *Tetrahedron* 39:3; Itakura *et al.*, 1984, *Annu. Rev. Biochem.* 53:323; Itakura *et al.*, 1984, *Science* 198:1056; Ike *et al.*, 1983 *Nucleic Acid Res.* 11:477).

In addition, libraries of segments of a marker protein can be used to generate a variegated population of polypeptides for screening and subsequent selection of variant marker proteins or segments thereof. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the

coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by
5 treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes amino terminal and internal fragments of various sizes of the protein of interest.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA
10 libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates
15 isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify variants of a protein of the invention (Arkin and Yourvan, 1992, *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.*, 1993, *Protein Engineering* 6(3):327- 331).

20 Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an
25 immunoglobulin molecule, (*i.e.*, such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, *e.g.*, an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an antibody which binds the protein, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the protein. Examples of an
30 immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and F(ab')₂ fragments.

An isolated protein of the invention or a fragment thereof can be used as an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10,
5 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the proteins of the invention, and encompasses at least one epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, *e.g.*, hydrophilic regions. Hydrophobicity
10 sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

An immunogen typically is used to prepare antibodies by immunizing a suitable (*i.e.* immunocompetent) subject such as a rabbit, goat, mouse, or other mammal
15 or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized protein or peptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent. Preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made
20 using a non-human host cell for recombinant expression of a protein of the invention. In such a manner, the resulting antibody compositions have reduced or no binding of human proteins other than a protein of the invention.

The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to
25 a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed against
30 a marker protein or fragment thereof.

Polyclonal antibodies can be prepared by immunizing a suitable subject with a protein of the invention as an immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. At an appropriate time after immunization, *e.g.*, when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies (mAb) by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell hybridoma technique (see Kozbor *et al.*, 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (see Cole *et al.*, pp. 77-96 In *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology*, Coligan *et al.* ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, *e.g.*, using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a protein of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J.* 12:725-734.

The invention also provides recombinant antibodies that specifically bind a protein of the invention. In preferred embodiments, the recombinant antibodies specifically binds a marker protein or fragment thereof. Recombinant antibodies include, but are not limited to, chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, single-chain antibodies and multi-specific antibodies. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.*, Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Single-chain antibodies have an antigen binding site and consist of single polypeptides. They can be produced by techniques known in the art, for example using methods described in Ladner *et. al* U.S. Pat. No. 4,946,778 (which is incorporated herein by reference in its entirety); Bird *et al.*, (1988) *Science* 242:423-426; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:1-9; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:97-105; and Huston *et al.*, (1991) *Methods in Enzymology Molecular Design and Modeling: Concepts and Applications* 203:46-88. Multi-specific antibodies are antibody molecules having at least two antigen-binding sites that specifically bind different antigens. Such molecules can be produced by techniques known in the art, for example using methods described in Segal, U.S. Patent No. 4,676,980 (the disclosure of which is incorporated herein by reference in its entirety); Holliger et al., (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Whitlow *et al.*, (1994) *Protein Eng.* 7:1017-1026 and U.S. Pat. No. 6,121,424.

Humanized antibodies are antibody molecules from non-human species having one or more complementarity determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, *e.g.*, Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu

et al. (1987) *J. Immunol.* 139:3521- 3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Cancer Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

More particularly, humanized antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes.

10 The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class

15 switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*,

20 U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be

25 generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, *e.g.*, a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers *et al.*, 1994, *Bio/technology* 12:899-903).

The antibodies of the invention can be isolated after production (*e.g.*,

30 from the blood or serum of the subject) or synthesis and further purified by well-known techniques. For example, IgG antibodies can be purified using protein A chromatography. Antibodies specific for a protein of the invention can be selected or

(*e.g.*, partially purified) or purified by, *e.g.*, affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, *i.e.*, one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein of the invention.

In a preferred embodiment, the substantially purified antibodies of the invention may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a protein of the invention. In a particularly preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a protein of the invention. In a more preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a marker protein.

An antibody directed against a protein of the invention can be used to isolate the protein by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the marker protein or fragment thereof (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (*e.g.* in an ovary-associated body fluid) as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by the

use of an antibody derivative, which comprises an antibody of the invention coupled to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish
5 peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol;
10 examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

Antibodies of the invention may also be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic treatment of human cancer patients, particularly those
15 having an ovarian cancer. In another preferred embodiment, antibodies that bind specifically to a marker protein or fragment thereof are used for therapeutic treatment. Further, such therapeutic antibody may be an antibody derivative or immunotoxin comprising an antibody conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any
20 agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof.
25 Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines
30 (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

The conjugated antibodies of the invention can be used for modifying a given biological response, for the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as ribosome-inhibiting protein (see Better et al., U.S. Patent No. 6,146,631, the disclosure of which is incorporated herein in its entirety), abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982).

Accordingly, in one aspect, the invention provides substantially purified antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. In various embodiments, the substantially purified antibodies of the invention, or fragments or derivatives thereof, can be human, non-human, chimeric and/or humanized antibodies. In another aspect, the invention provides non-human antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat

- 64 -

antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies. In still a further aspect, the invention provides monoclonal antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a pharmaceutical composition comprising an antibody of the invention and a pharmaceutically acceptable carrier. In preferred embodiments, the pharmaceutical composition contains an antibody of the invention, a therapeutic moiety, and a pharmaceutically acceptable carrier.

15 III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a marker protein (or a portion of such a protein). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, namely expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective

retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell.

5 This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression
10 of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, *Methods in Enzymology: Gene Expression Technology* vol.185,
15 Academic Press, San Diego, CA (1991). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the
20 host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors of the invention can be designed for
25 expression of a marker protein or a segment thereof in prokaryotic (*e.g.*, *E. coli*) or eukaryotic cells (*e.g.*, insect cells {using baculovirus expression vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

30 Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a

protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification.

5 Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX
10 (Pharmacia Biotech Inc; Smith and Johnson, 1988, *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors
15 include pTrc (Amann *et al.*, 1988, *Gene* 69:301-315) and pET 11d (Studier *et al.*, p. 60-89, In *Gene Expression Technology: Methods in Enzymology* vol.185, Academic Press, San Diego, CA, 1991). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter
20 mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave
25 the recombinant protein (Gottesman, p. 119-128, In *Gene Expression Technology: Methods in Enzymology* vol. 185, Academic Press, San Diego, CA, 1990. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, 1992, *Nucleic Acids Res.* 20:2111-2118).
30 Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari *et al.*, 1987, *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, 1982, *Cell* 30:933-943), pJRY88 (Schultz *et al.*, 1987, *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.*, 1983, *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers, 1989, *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987, *Nature* 329:840) and pMT2PC (Kaufman *et al.*, 1987, *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook *et al.*, *supra*.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert *et al.*, 1987, *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton, 1988, *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989, *EMBO J.* 8:729-733) and immunoglobulins (Banerji *et al.*, 1983, *Cell* 33:729-740; Queen and Baltimore, 1983, *Cell* 33:741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle, 1989, *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund *et al.*, 1985, *Science* 230:912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters

(Kessel and Gruss, 1990, *Science* 249:374-379) and the α -fetoprotein promoter (Camper and Tilghman, 1989, *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory
5 sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the
10 antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue-specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency
15 regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub *et al.*, 1986, *Trends in Genetics*, Vol. 1(1).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host
20 cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term
25 as used herein.

A host cell can be any prokaryotic (*e.g.*, *E. coli*) or eukaryotic cell (*e.g.*, insect cells, yeast or mammalian cells).

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms
30 "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection,

lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells
5 may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid
10 can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a marker protein or a segment thereof. Accordingly, the invention further provides methods for producing a marker protein or a segment
15 thereof using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a marker protein or a segment thereof has been introduced) in a suitable medium such that the is produced. In another embodiment, the method further comprises isolating the a marker protein or a segment thereof from the medium or the
20 host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequences encoding a marker protein or a segment thereof have been introduced. Such host cells can then be used to
25 create non-human transgenic animals in which exogenous sequences encoding a marker protein of the invention have been introduced into their genome or homologous recombinant animals in which endogenous gene(s) encoding a marker protein have been altered. Such animals are useful for studying the function and/or activity of the marker protein and for identifying and/or evaluating modulators of marker protein. As used
30 herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human

primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a nucleic acid encoding a marker protein into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

To create an homologous recombinant animal, a vector is prepared which contains at least a portion of a gene encoding a marker protein into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (*i.e.*, no longer encodes a

functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, *e.g.*, Thomas and Capecchi, 1987, *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (see, *e.g.*, Li *et al.*, 1992, *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see, *e.g.*, Bradley, *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, Ed., IRL, Oxford, 1987, pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.*, 1991, *Science* 251:1351-1355). If a *cre/loxP* recombinase system is used to regulate expression of the

- 72 -

transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.* (1997) *Nature* 385:810-813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

10 IV. Pharmaceutical Compositions

The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier.

15 As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent
20 is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a marker nucleic acid or
25 protein. Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or
30 activity of a marker nucleic acid or protein and one or more additional active compounds.

The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (*e.g.*, stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (*e.g.*, peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

The test compounds of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, *e.g.*, Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott
5 and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al*, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a protein encoded by or
10 corresponding to a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a protein encoded by or corresponding to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a protein can be accomplished, for example, by coupling the compound with a
15 radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (*e.g.*, marker substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically
20 labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the expression of a marker or the activity
25 of a protein encoded by or corresponding to a marker, or a biologically active portion thereof. In all likelihood, the protein encoded by or corresponding to the marker can, *in vivo*, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids. For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as "binding partners" or marker
30 "substrate".

One necessary embodiment of the invention in order to facilitate such screening is the use of a protein encoded by or corresponding to marker to identify the protein's natural *in vivo* binding partners. There are many ways to accomplish this which are known to one skilled in the art. One example is the use of the marker protein as "bait protein" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al*, 1993, *Cell* 72:223-232; Madura *et al*, 1993, *J. Biol. Chem.* 268:12046-12054; Bartel *et al*, 1993, *Biotechniques* 14:920-924; Iwabuchi *et al*, 1993 *Oncogene* 8:1693-1696; Brent WO94/10300) in order to identify other proteins which bind to or interact with the marker (binding partners) and, therefore, are possibly involved in the natural function of the marker. Such marker binding partners are also likely to be involved in the propagation of signals by the marker protein or downstream elements of a marker protein-mediated signaling pathway. Alternatively, such marker protein binding partners may also be found to be inhibitors of the marker protein.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that encodes a marker protein fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a marker-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be readily detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the marker protein.

In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (*e.g.*, affect either positively or negatively) interactions between a marker protein and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof.

- 76 -

Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is an ovarian cancer marker protein identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be
5 supplied from any source.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker protein and its binding partner involves preparing a reaction mixture containing the marker protein and its binding partner under conditions and for a time sufficient to allow the two products to interact
10 and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker protein and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The
15 formation of any complexes between the marker protein and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker protein and its binding partner. Conversely, the formation of more complex in the presence of compound than in the
20 control reaction indicates that the compound may enhance interaction of the marker protein and its binding partner.

The assay for compounds that interfere with the interaction of the marker protein with its binding partner may be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the marker protein or its binding
25 partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction between the marker proteins and the binding partners
30 (*e.g.*, by competition) can be identified by conducting the reaction in the presence of the test substance, *i.e.*, by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test

compounds that disrupt preformed complexes, *e.g.*, compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

5 In a heterogeneous assay system, either the marker protein or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to
10 one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker protein or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

15 In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then
20 combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (*e.g.*, physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described
25 above. Alternatively, the complexes can be dissociated from the matrix, and the level of marker binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker protein or a marker protein binding partner can be immobilized utilizing conjugation of biotin and
30 streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of

streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the protein-immobilized surfaces can be prepared in advance and stored.

In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (e.g., by washing) and any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed.

Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, e.g., a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

In an alternate embodiment of the invention, a homogeneous assay may be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993 Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration

chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.*, Heegaard, 1998, *J Mol. Recognit.* 11:141-148; Hage and Tweed, 1997, *J. Chromatogr. B. Biomed. Sci. Appl.*, 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, *e.g.*, Ausubel *et al* (eds.), as described in : Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, *e.g.*, Ausubel *et al* (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be compared, thus offering information about the ability of the compound to modulate interactions between the marker protein and its binding partner.

Also within the scope of the present invention are methods for direct detection of interactions between the marker protein and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without

further sample manipulation. For example, the technique of fluorescence energy transfer may be utilized (see, *e.g.*, Lakowicz *et al*, U.S. Patent No. 5,631,169; Stavrianopoulos *et al*, U.S. Patent No. 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (*e.g.*, marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (*e.g.*, marker or test compound), which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of marker mRNA or protein in the cell, is determined. The level of expression of marker mRNA or protein in the presence of the candidate compound is compared to the level of expression of marker mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression

in the cells can be determined by methods described herein for detecting marker mRNA or protein.

In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using
5 a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a marker protein can be further confirmed *in vivo*, *e.g.*, in a whole animal model for cellular transformation and/or tumorigenesis.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to
10 further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, an marker modulating agent, an antisense marker nucleic acid molecule, an marker-specific antibody, or an marker-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as
15 described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

It is understood that appropriate doses of small molecule agents and protein or polypeptide agents depends upon a number of factors within the knowledge of
20 the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of these agents will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the agent to have upon the nucleic acid or polypeptide of the invention. Exemplary doses of a small
25 molecule include milligram or microgram amounts per kilogram of subject or sample weight (*e.g.* about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). Exemplary doses of a protein or polypeptide include gram, milligram or microgram amounts per kilogram of
30 subject or sample weight (*e.g.* about 1 microgram per kilogram to about 5 grams per kilogram, about 100 micrograms per kilogram to about 500 milligrams per kilogram, or about 1 milligram per kilogram to about 50 milligrams per kilogram). It is furthermore

understood that appropriate doses of one of these agents depend upon the potency of the agent with respect to the expression or activity to be modulated. Such appropriate doses can be determined using the assays described herein. When one or more of these agents is to be administered to an animal (*e.g.* a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher can, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediamine-tetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy

syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can
5 be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid,
10 thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

15 Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium,
20 and then incorporating the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

25 Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid
30 carrier is applied orally and swished and expectorated or swallowed.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a
5 lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the
10 form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally
15 known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

20 The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled
25 release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova
30 Pharmaceuticals, Inc. Liposomal suspensions (including liposomes having monoclonal antibodies incorporated therein or thereon) can also be used as pharmaceutically

acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit
5 form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound
10 and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies
15 and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (*e.g.*, into the ovarian epithelium). A method for lipidation of antibodies is described by Cruikshank *et al.* (1997) *J. Acquired Immune*
20 *Deficiency Syndromes and Human Retrovirology* 14:193.

The invention also provides vaccine compositions for the prevention and/or treatment of ovarian cancer. The invention provides ovarian cancer vaccine compositions in which a protein of a marker of Table 1, or a combination of proteins of the markers of Table 1, are introduced into a subject in order to stimulate an immune
25 response against the ovarian cancer. The invention also provides ovarian cancer vaccine compositions in which a gene expression construct, which expresses a marker or fragment of a marker identified in Table 1, is introduced into the subject such that a protein or fragment of a protein encoded by a marker of Table 1 is produced by transfected cells in the subject at a higher than normal level and elicits an immune
30 response.

In one embodiment, an ovarian cancer vaccine is provided and employed as an immunotherapeutic agent for the prevention of ovarian cancer. In another embodiment, an ovarian cancer vaccine is provided and employed as an immunotherapeutic agent for the treatment of ovarian cancer.

5 By way of example, an ovarian cancer vaccine comprised of the proteins of the markers of Table 1, may be employed for the prevention and/or treatment of ovarian cancer in a subject by administering the vaccine by a variety of routes, *e.g.*, intradermally, subcutaneously, or intramuscularly. In addition, the ovarian cancer vaccine can be administered together with adjuvants and/or immunomodulators to boost
10 the activity of the vaccine and the subject's response. In one embodiment, devices and/or compositions containing the vaccine, suitable for sustained or intermittent release could be, implanted in the body or topically applied thereto for the relatively slow release of such materials into the body. The ovarian cancer vaccine can be introduced along with immunomodulatory compounds, which can alter the type of immune
15 response produced in order to produce a response which will be more effective in eliminating the cancer.

In another embodiment, an ovarian cancer vaccine comprised of an expression construct of the markers of Table 1, may be introduced by injection into muscle or by coating onto microprojectiles and using a device designed for the purpose
20 to fire the projectiles at high speed into the skin. The cells of the subject will then express the protein(s) or fragments of proteins of the markers of Table 1 and induce an immune response. In addition, the ovarian cancer vaccine may be introduced along with expression constructs for immunomodulatory molecules, such as cytokines, which may increase the immune response or modulate the type of immune response produced in
25 order to produce a response which will be more effective in eliminating the cancer.

The marker nucleic acid molecules of the present invention can also be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470), or by stereotactic injection (see, *e.g.*, Chen *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:3054-3057).
30 The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively,

where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.* retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or
5 dispenser together with instructions for administration.

V. Predictive Medicine

The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical
10 trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing ovarian cancer. Such assays can be used for prognostic or predictive purposes to thereby
15 prophylactically treat an individual prior to the onset of the cancer.

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs or other compounds administered either to inhibit ovarian cancer or to treat or prevent any other disorder {*i.e.* in order to understand any ovarian carcinogenic effects that such treatment may have}) on the expression or activity of a
20 marker of the invention in clinical trials. These and other agents are described in further detail in the following sections.

A. Diagnostic Assays

An exemplary method for detecting the presence or absence of a marker
25 protein or nucleic acid in a biological sample involves obtaining a biological sample (*e.g.* an ovary-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (*e.g.*, mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a
30 biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of a marker protein include enzyme linked immunosorbent

assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of genomic DNA include Southern hybridizations.

Furthermore, *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein or fragment thereof. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay.

There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polyethylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (*e.g.*, by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for example, Lakowicz *et al.*, U.S. Patent No. 5,631,169; Stavrianopoulos, *et al.*, U.S. Patent No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter).

In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis (BIA) (see, *e.g.*, Sjolander, S. and Urbaniczky, C., 1991, *Anal. Chem.* 63:2338-2345

and Szabo *et al.*, 1995, *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)),
5 resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase.

10 In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a series of centrifugal steps, due to the different
15 sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., 1993, *Trends Biochem Sci.* 18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel
20 filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange
25 chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.*, Heegaard, N.H., 1998, *J. Mol. Recognit.* Winter 11(1-6):141-8; Hage, D.S., and Tweed, S.A. *J Chromatogr B Biomed Sci Appl* 1997 Oct 10;699(1-2):499-525). Gel electrophoresis may also be employed to separate complexed assay components from unbound components (see, *e.g.*, Ausubel *et al.*, ed.,
30 *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1987-1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the

electrophoretic process, non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

In a particular embodiment, the level of marker mRNA can be
5 determined both by *in situ* and by *in vitro* formats in a biological sample using methods known in the art. The term "biological sample" is intended to include tissues, cells, biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and fluids present within a subject. Many expression detection methods use isolated RNA. For *in vitro* methods, any RNA isolation technique that does not select against the
10 isolation of mRNA can be utilized for the purification of RNA from ovarian cells (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No.
15 4,843,155).

The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule
20 (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the
25 diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

In one format, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an
30 alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled

artisan can readily adapt known mRNA detection methods for use in detecting the level of mRNA encoded by the markers of the present invention.

An alternative method for determining the level of mRNA marker in a sample involves the process of nucleic acid amplification, *e.g.*, by rtPCR (the
5 experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany, 1991, *Proc. Natl. Acad. Sci. USA*, 88:189-193), self sustained sequence replication (Guatelli *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.*, 1988, *Bio/Technology* 6:1197), rolling
10 circle replication (Lizardi *et al.*, U.S. Patent No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. As used herein, amplification primers are defined as being
15 a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid
20 molecule comprising the nucleotide sequence flanked by the primers.

For *in situ* methods, mRNA does not need to be isolated from the ovarian cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that
25 encodes the marker.

As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a
30 gene that is not a marker, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the

expression level in one sample, *e.g.*, a patient sample, to another sample, *e.g.*, a non-ovarian cancer sample, or between samples from different sources.

Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a marker, the level of
5 expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the
10 test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.

Preferably, the samples used in the baseline determination will be from ovarian cancer or from non-ovarian cancer cells of ovarian tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found
15 in normal tissues as a mean expression score aids in validating whether the marker assayed is ovarian specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from ovarian cells provides a means for grading the severity of the ovarian cancer state.

20 In another embodiment of the present invention, a marker protein is detected. A preferred agent for detecting marker protein of the invention is an antibody capable of binding to such a protein or a fragment thereof, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment or derivatives thereof (*e.g.*, Fab or F(ab')₂) can be used.
25 The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody
30 and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

Proteins from ovarian cells can be isolated using techniques that are well known to those of skill in the art. The protein isolation methods employed can, for example, be such as those described in Harlow and Lane (Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York).

A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can readily adapt known protein/antibody detection methods for use in determining whether ovarian cells express a marker of the present invention.

In one format, antibodies, or antibody fragments or derivatives, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present invention. For example, protein isolated from ovarian cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on the solid support can then be detected by conventional means.

The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample (e.g. an ovary-associated body fluid such as a urine sample). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing ovarian cancer. For example, the kit can comprise a labeled compound or agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or

mRNA in the sample (*e.g.*, an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for interpreting the results obtained using the kit.

For antibody-based kits, the kit can comprise, for example: (1) a first
5 antibody (*e.g.*, attached to a solid support) which binds to a marker protein; and, optionally, (2) a second, different antibody which binds to either the protein or the first antibody and is conjugated to a detectable label.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an
oligonucleotide, *e.g.*, a detectably labeled oligonucleotide, which hybridizes to a nucleic
10 acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. The kit can also comprise, *e.g.*, a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components necessary for detecting the detectable label (*e.g.*, an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and
15 compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

B. Pharmacogenomics

20 Agents or modulators which have a stimulatory or inhibitory effect on expression of a marker of the invention can be administered to individuals to treat (prophylactically or therapeutically) ovarian cancer in the patient. In conjunction with such treatment, the pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of
25 the individual may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (*e.g.*, drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such
30 pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the level of expression of a marker of the invention in an

individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, *e.g.*, Linder (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body are referred to as "altered drug action." Genetic conditions transmitted as single factors altering the way the body acts on drugs are referred to as "altered drug metabolism". These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the
5 identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a modulator of expression of a marker of the invention.

10 C. Monitoring Clinical Trials

Monitoring the influence of agents (*e.g.*, drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for ovarian
15 cancer. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one
20 or more selected markers of the invention in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi)
25 altering the administration of the agent to the subject accordingly. For example, increased administration of the agent can be desirable to increase expression of the marker(s) to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent can be desirable to decrease expression of the marker(s) to lower levels than detected, *i.e.*, to decrease the
30 effectiveness of the agent.

D. Electronic Apparatus Readable Media and Arrays

Electronic apparatus readable media comprising a marker of the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be
5 read and accessed directly by an electronic apparatus. Such media can include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or
10 configured for having recorded thereon a marker of the present invention.

As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local
15 area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can
20 readily adopt any of the presently known methods for recording information on known media to generate manufactures comprising the markers of the present invention.

A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. For example, the marker nucleic acid sequence can be represented in a word
25 processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of data processor structuring formats (*e.g.*, text file or database) may be employed in order to obtain or create a medium having recorded thereon the the markers
30 of the present invention.

By providing the markers of the invention in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

The present invention therefore provides a medium for holding instructions for performing a method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has ovarian cancer or a pre-disposition to ovarian cancer and/or recommending a particular treatment for ovarian cancer or pre-ovarian cancer condition.

The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the presence or absence of the marker, determining whether the subject has ovarian cancer or a pre-disposition to ovarian cancer, and/or recommending a particular treatment for the ovarian cancer or pre-ovarian cancer condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

The present invention also provides in a network, a method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer associated with a marker, said method comprising the steps of receiving information associated with the marker receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or ovarian cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a ovarian cancer or a pre-disposition to ovarian cancer. The method may further comprise the step of

recommending a particular treatment for the ovarian cancer or pre-ovarian cancer condition.

The present invention also provides a business method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer, said method comprising the steps of receiving information associated with the marker, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or ovarian cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has ovarian cancer or a pre-disposition to ovarian cancer. The method may further comprise the step of recommending a particular treatment for the ovarian cancer or pre-ovarian cancer condition.

The invention also includes an array comprising a marker of the present invention. The array can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7600 genes can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of genes specifically expressed in one or more tissues.

In addition to such qualitative determination, the invention allows the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be grouped on the basis of their tissue expression *per se* and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined. Such a determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the invention provides an assay to determine the molecular basis of the undesirable effect and thus provides the opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be

determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of ovarian cancer, progression of ovarian cancer, and processes, such a cellular transformation associated with ovarian cancer.

The array is also useful for ascertaining the effect of the expression of a gene on the expression of other genes in the same cell or in different cells. This provides, for example, for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

The array is also useful for ascertaining differential expression patterns of one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

15

E. Surrogate Markers

The markers of the invention may serve as surrogate markers for one or more disorders or disease states or for conditions leading up to disease states, and in particular, ovarian cancer. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (*e.g.*, with the presence or absence of a tumor). The presence or quantity of such markers is independent of the disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (*e.g.*, early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is reached (*e.g.*, an assessment of cardiovascular disease may be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection may be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate

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25
30

markers in the art include: Koomen *et al.* (2000) *J. Mass. Spectrom.* 35: 258-264; and James (1994) *AIDS Treatment News Archive* 209.

The markers of the invention are also useful as pharmacodynamic markers. As used herein, a “pharmacodynamic marker” is an objective biochemical
5 marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker may be indicative of the concentration of the drug in a
10 biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or
15 quantity of the marker is indicative of the relative breakdown rate of the drug *in vivo*. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more
20 readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic marker may offer mechanism-based
25 prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers in the art include: Matsuda *et al.* US 6,033,862; Hattis *et al.* (1991) *Env. Health Perspect.* 90: 229-238; Schentag (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S21-S24; and Nicolau (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S16-S20.

VI. Experimental Protocol for all OV markers and M352 - M360

A. Identification of markers

The markers of the present invention were identified by transcriptional
5 profiling using mRNA from 9 normal ovarian epithelia, 11 stage I/II ovarian cancer
tumors and 25 stage III/IV tumors. Clones having expression at least two-fold higher in
ovarian tumors as compared to their expression in non-ovarian tumor tissues in at least 4
tumor samples were selected to have their protein-encoding transcript sequences
determined.

10

B. Identification of Markers and Assembly of Their Sequences

Clones which displayed an increase in expression in ovarian tumor
samples over the corresponding average expression of non-tumor samples were used for
further study. Briefly, BLAST analysis, against both public and proprietary sequence
15 databases, of EST sequences known to be associated with each clone was performed,
either directly or in the context of automatically, high-stringency assembled contiguous
sequences. An identification of protein sequence corresponding to the clone was
accomplished by obtaining one of the following:

a) a direct match between the protein sequence and at least one EST
20 sequence in one of its 6 possible translations;

b) a direct match between the nucleotide sequence for the mRNA
corresponding to the protein sequence and at least one EST sequence;

c) a match between the protein sequence and a contiguous assembly
(contig) of the EST sequences with other available EST sequences in the databases in
25 one of its 6 possible translations; or

d) a match between the nucleotide sequence for the mRNA
corresponding to the protein sequence and a contiguous assembly of the EST sequences
with other available EST sequences in the databases in one of its 6 possible translations.

C. Identification of Markers Having Newly-Identified Nucleotide and Amino Acid Sequences.

The markers of Table 2 include newly-identified amino acid sequences.

5 These sequences were found to be novel based on one of the following criteria:

a) the protein sequence found within available public databases was incomplete or erroneous, leading to the construction of an additional

completed/corrected protein sequence that is not found as such in the public domain;

b) based on nucleotide evidence, variants of the protein sequence were
10 additionally constructed that are not found as such in the public domain; or

c) the contig for the EST sequences did not match any known protein, so that a novel protein sequence was derived from an open reading frame of the contig.

15 VII. Experimental Protocol for M68, M103, M138, M185, M312, M327-M328, M400, M430-M480, M559, M571-M573, M575-M576, M578-M583, M585-594, and M604-M617

A. Identification of Markers and Assembly of Their Sequences

20 The markers of the present invention were identified by transcription profiling using mRNA from 67 ovarian tumors of various histotypes and stage and 96 non-ovarian tumor tissues including normal ovarian epithelium, benign conditions, other normal tissues, and other abnormal tissues. Clones having expression at least three-fold higher in at least 10% of ovarian tumors, as compared to their expression in non-ovarian
25 tumor tissue, were designated as ovarian cancer specific markers. These cDNA clones were selected to have their protein-encoding transcript sequences determined. Briefly, BLAST analysis, against both public and proprietary sequence databases, of EST sequences known to be associated with each clone was performed, either directly or in the context of automatically, high-stringency assembled contiguous sequences. An
30 identification of protein sequence corresponding to the clone was accomplished by obtaining one of the following:

a) a direct match between the protein sequence and at least one EST sequence in one of its 6 possible translations;

b) a direct match between the nucleotide sequence for the mRNA corresponding to the protein sequence and at least one EST sequence;

c) a match between the protein sequence and a contiguous assembly (contig) of the EST sequences with other available EST sequences in the databases in
5 one of its 6 possible translations; or

d) a match between the nucleotide sequence for the mRNA corresponding to the protein sequence and a contiguous assembly of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations.

10 B. Identification of Markers Having Newly-Identified Amino Acid Sequences.

The markers of Table 2 include newly-identified amino acid sequences. These sequences were found to be novel based on one of the following criteria:

- a) the protein sequence found within available public databases was
15 incomplete or erroneous, leading to the construction of an additional completed/corrected protein sequence that is not found as such in the public domain;
- b) based on nucleotide evidence, variants of the protein sequence were additionally constructed that are not found as such in the public domain; or
- c) the contig for the EST sequences did not match any known protein, so
20 that a novel protein sequence was derived from an open reading frame of the contig.

VIII. Gene Expression Analysis

Total RNA from normal human tissue was obtained from commercial sources. The integrity of the RNA was verified by agarose gel electrophoresis and
25 ethidium bromide staining. Cell lines were purchased from ATCC and grown under the conditions recommended by ATCC. Total RNA from a number of various cell lines was prepared using commercial kits (Qiagen). First strand cDNA was prepared using oligo-dT primer and standard conditions. Each RNA preparation was treated with DNase I (Ambion) at 37°C for 1 hour.

30 Novel gene expression was measured by TaqMan[®] quantitative PCR (Perkin Elmer Applied Biosystems) in cDNA prepared from the following normal human tissues: heart, kidney, skeletal muscle, pancreas, skin, dorsal root ganglion,

- 106 -

breast, ovary, prostate, salivary glands, lung, colon, liver and lymph node. Figure 1 graphically represents the results of the TaqMan® expression study. The columns labelled A to V depict the expression level observed for OV88 in the following tissues:

- Column A: Heart, normal tissue
- 5 Column B: Heart, CHF tissue
- Column C: Kidney, normal tissue
- Column D: Skeletal muscle, normal tissue
- Column E: Pancreas, normal tissue
- Column F: Skin, normal tissue
- 10 Column G: Dorsal root, normal tissue
- Column H: Breast, normal tissue
- Column I: Breast, tumor tissue
- Column J: Ovary, normal tissue
- Column K: Ovary, tumor tissue
- 15 Column L: Prostate, normal tissue
- Column M: Prostate, tumor tissue
- Column N: Salivary glands, normal tissue
- Column O: Lung, normal tissue
- Column P: Lung, tumor tissue
- 20 Column Q: Lung, COPD tissue
- Column R: Colon, IBD tissue
- Column S: Liver, normal tissue
- Column T: Liver fibrosis
- Column U: Lymph node, normal tissue
- 25 Column V: Positive control

IX. Summary of the Data Provided in the Tables

- Tables 1-3 list the markers of the present invention. In the Tables the markers are identified with a name ("Marker"), the name the gene is commonly known
- 30 by, if applicable ("Gene Name"), the Sequence Listing identifier of the cDNA sequence of a nucleotide transcript encoded by or corresponding to the marker ("SEQ ID NO (nts)"), the Sequence Listing identifier of the amino acid sequence of a protein encoded

- 107 -

by the nucleotide transcript ("SEQ ID NO (AAs)"), and the location of the protein coding sequence within the cDNA sequence ("CDS").

Table 1 lists all of the markers of the invention, which are over-expressed in ovarian cancer cells compared to normal (*i.e.*, non-cancerous) ovarian cells and
5 comprises markers listed in Tables 2 and 3. Table 2 lists newly-identified nucleotide and amino acid sequences useful as ovarian cancer markers. Table 3 lists newly-identified nucleotide sequences useful as ovarian cancer markers.

Other Embodiments

10 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims:

What is claimed:

1. A method of assessing whether a patient is afflicted with ovarian cancer, the method comprising comparing:
 - 5 a) the level of expression of a marker in a patient sample, wherein the marker is selected from Table 1, and
 - b) the normal level of expression of the marker in a control non-ovarian cancer sample,
- 10 wherein a significant increase in the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with ovarian cancer.

SEQUENCE LISTING

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Assessment, Prevention, and Therapy of Ovarian Cancer

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65          70          75          80
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Lys Gly Gln Asp Gly Ile Gly Ser Lys Ala Glu Lys Thr Leu Gly Asp
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Asp Pro Glu Lys Pro Gln Leu Gly Met Ile Asp Arg Trp Tyr His Pro
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Asp	Ala	Ile	Glu	Gln	Phe	Met	Lys	Leu	Tyr	Glu	Glu	Lys	Thr	Gly	Asn
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Ile	Lys	Met	Ile	P											

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 Ile Lys Val Val Asp Arg Asp Ser Glu Glu Ala Glu Ile Ile Arg Lys
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      35             40             45
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      50             55             60
Asn Ala Gln Arg Gln Asp Ile Ala Phe Ala Tyr Gln Arg Arg Thr Lys
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Leu Glu Ser Ile Arg Lys Glu Val Lys Gly Asp Leu Glu Asn Ala Phe
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Leu Asn Leu Val Gln Cys Ile Gln Asn Lys Pro Leu Tyr Phe Ala Asp
      260            265            270
Arg Leu Tyr Asp Ser Met Lys Gly Lys Gly Thr Arg Asp Lys Val Leu
      275            280            285
Ile Arg Ile Met Val Ser Arg Ser Glu Val Asp Met Leu Lys Ile Arg
      290            295            300
Ser Glu Phe Lys Arg Lys Tyr Gly Lys Ser Leu Tyr Tyr Tyr Ile Gln
      305            310            315            320
Gln Asp Thr Lys Gly Asp Tyr Gln Lys Ala Leu Leu Tyr Leu Cys Gly
      325            330            335
Gly Asp Asp

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<210> 7
 <211> 1362
 <212> DNA
 <213> Homo sapiens

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 agccatcaag accaaaggtg tggatgaggt caccattgtc aacattttga ccaaccgcag 240
 caatgcacag agacaggata ttgccttcgc ctaccagaga aggacaaaaa aggaacttgc 300
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<210> 8
 <211> 339
 <212> PRT
 <213> Homo sapiens

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 Phe Asp Ala Glu Arg Asp Ala Leu Asn Ile Glu Thr Ala Ile Lys Thr
 35 40 45
 Lys Gly Val Asp Glu Val Thr Ile Val Asn Ile Leu Thr Asn Arg Ser
 50 55 60
 Asn Ala Gln Arg Gln Asp Ile Ala Phe Ala Tyr Gln Arg Arg Thr Lys
 65 70 75 80
 Lys Glu Leu Ala Ser Ala Leu Lys Ser Ala Leu Ser Gly His Leu Glu
 85 90 95
 Thr Val Ile Leu Gly Leu Leu Lys Thr Pro Ala Gln Tyr Asp Ala Ser
 100 105 110
 Glu Leu Lys Ala Ser Met Lys Gly Leu Gly Thr Asp Glu Asp Ser Leu
 115 120 125
 Ile Glu Ile Ile Cys Ser Arg Thr Asn Gln Glu Leu Gln Glu Ile Asn
 130 135 140
 Arg Val Tyr Lys Glu Met Tyr Lys Thr Asp Leu Glu Lys Asp Ile Ile
 145 150 155 160
 Ser Asp Thr Ser Gly Asp Phe Arg Lys Leu Met Val Ala Leu Ala Lys
 165 170 175

Gly Arg Arg Ala Glu Asp Gly Ser Val Ile Asp Tyr Glu Leu Ile Asp
 180 185 190
 Gln Asp Ala Arg Asp Leu Tyr Asp Ala Gly Val Lys Arg Lys Gly Thr
 195 200 205
 Asp Val Pro Lys Trp Ile Ser Ile Met Thr Glu Arg Ser Val Pro His
 210 215 220
 Leu Gln Lys Val Phe Asp Arg Tyr Lys Ser Tyr Ser Pro Tyr Asp Met
 225 230 235 240
 Leu Glu Ser Ile Arg Lys Glu Val Lys Gly Asp Leu Glu Asn Ala Phe
 245 250 255
 Leu Asn Leu Val Gln Cys Ile Gln Asn Lys Pro Leu Tyr Phe Ala Asp
 260 265 270
 Arg Leu Tyr Asp Ser Met Lys Gly Lys Gly Thr Arg Asp Lys Val Leu
 275 280 285
 Ile Arg Ile Met Val Ser Arg Ser Glu Val Asp Met Leu Lys Ile Arg
 290 295 300
 Ser Glu Phe Lys Arg Lys Tyr Gly Lys Ser Leu Tyr Tyr Tyr Ile Gln
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 Gly Asp Asp

<210> 9

<211> 1982

<212> DNA

<213> Homo sapiens

<400> 9

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tgtgctaaaa atacttttta aaatcaattt tgttgattgt agtaatttct atttgcactg 1920
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<210> 10

<211> 321

<212> PRT

<213> Homo sapiens

<400> 10

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      35          40          45
Ala Gln Arg Gln Glu Ile Arg Thr Ala Tyr Lys Ser Thr Ile Gly Arg
      50          55          60
Asp Leu Ile Asp Asp Leu Lys Ser Glu Leu Ser Gly Asn Phe Glu Gln
      65          70          75          80
Val Ile Val Gly Met Met Thr Pro Thr Val Leu Tyr Asp Val Gln Glu
      85          90          95
Leu Arg Arg Ala Met Lys Gly Ala Gly Thr Asp Glu Gly Cys Leu Ile
      100          105          110
Glu Ile Leu Ala Ser Arg Thr Pro Glu Glu Ile Arg Arg Ile Ser Gln
      115          120          125
Thr Tyr Gln Gln Gln Tyr Gly Arg Ser Leu Glu Asp Asp Ile Arg Ser
      130          135          140
Asp Thr Ser Phe Met Phe Gln Arg Val Leu Val Ser Leu Ser Ala Gly
      145          150          155          160
Gly Arg Asp Glu Gly Asn Tyr Leu Asp Asp Ala Leu Val Arg Gln Asp
      165          170          175
Ala Gln Asp Leu Tyr Glu Ala Gly Glu Lys Lys Trp Gly Thr Asp Glu
      180          185          190
Val Lys Phe Leu Thr Val Leu Cys Ser Arg Asn Arg Asn His Leu Leu
      195          200          205
His Val Phe Asp Glu Tyr Lys Arg Ile Ser Gln Lys Asp Ile Glu Gln
      210          215          220
Ser Ile Lys Ser Glu Thr Ser Gly Ser Phe Glu Asp Ala Leu Leu Ala
      225          230          235          240
Ile Val Lys Cys Met Arg Asn Lys Ser Ala Tyr Phe Ala Glu Lys Leu
      245          250          255
Tyr Lys Ser Met Lys Gly Leu Gly Thr Asp Asp Asn Thr Leu Ile Arg
      260          265          270
Val Met Val Ser Arg Ala Glu Ile Asp Met Leu Asp Ile Arg Ala His
      275          280          285
Phe Lys Arg Leu Tyr Gly Lys Ser Leu Tyr Ser Phe Ile Lys Gly Asp
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Thr Ser Gly Asp Tyr Arg Lys Val Leu Leu Val Leu Cys Gly Gly Asp
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<210> 11

<211> 1316
 <212> DNA
 <213> Homo sapiens

<400> 11

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<210> 12
 <211> 265
 <212> PRT
 <213> Homo sapiens

<400> 12

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 20          25          30
Leu Lys Trp Pro Ser Ala Leu Pro Thr Ile Leu Gln Ile Ala Leu Ala
 35          40          45
Phe Gly Leu Ala Ile Gly Thr Leu Ala Gln Ala Leu Gly Pro Val Ser
 50          55          60
Gly Gly His Ile Asn Pro Ala Ile Thr Leu Ala Leu Leu Val Gly Asn
 65          70          75          80
Gln Ile Ser Leu Leu Arg Ala Phe Phe Tyr Val Ala Ala Gln Leu Val
 85          90          95
Gly Ala Ile Ala Gly Ala Gly Ile Leu Tyr Gly Val Ala Pro Leu Asn
100          105          110
Ala Arg Gly Asn Leu Ala Val Asn Ala Leu Asn Asn Asn Thr Thr Gln
115          120          125
Gly Gln Ala Met Val Val Glu Leu Ile Leu Thr Phe Gln Leu Ala Leu
130          135          140
Cys Ile Phe Ala Ser Thr Asp Ser Arg Arg Thr Ser Pro Val Gly Ser
145          150          155          160
Pro Ala Leu Ser Ile Gly Leu Ser Val Thr Leu Gly His Leu Val Gly
165          170          175
Ile Tyr Phe Thr Gly Cys Ser Met Asn Pro Ala Arg Ser Phe Gly Pro
180          185          190
  
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15

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Gly	Pro	Ile	Val	Gly	Ala	Val	Leu	Ala	Ala	Ile	Leu	Tyr	Phe	Tyr	Leu
	210					215					220				
Leu	Phe	Pro	Asn	Ser	Leu	Ser	Leu	Ser	Glu	Arg	Val	Ala	Ile	Ile	Lys
225					230					235					240
Gly	Thr	Tyr	Glu	Pro	Asp	Glu	Asp	Trp	Glu	Glu	Gln	Arg	Glu	Glu	Arg
				245					250					255	
Lys	Lys	Thr	Met	Glu	Leu	Thr	Thr	Arg							
			260					265							

<210> 13
 <211> 1653
 <212> DNA
 <213> Homo sapiens

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<210> 14
 <211> 464
 <212> PRT
 <213> Homo sapiens

<400> 14
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		35					40					45			
Leu	Asp	His	Gln	Arg	Leu	Leu	Glu	Tyr	Leu	Lys	Tyr	Thr	Leu	Asp	Gln
	50					55					60				
Tyr	Val	Glu	Asn	Asp	Tyr	Thr	Ile	Val	Tyr	Phe	His	Tyr	Gly	Leu	Asn
65					70					75					80
Ser	Arg	Asn	Lys	Pro	Ser	Leu	Gly	Trp	Leu	Gln	Ser	Ala	Tyr	Lys	Glu
				85					90					95	
Phe	Asp	Arg	Lys	Asp	Gly	Asp	Leu	Thr	Met	Trp	Pro	Arg	Leu	Val	Ser
			100					105					110		
Asn	Ser	Lys	Leu	Lys	Arg	Ser	Ser	His	Leu	Ser	Leu	Pro	Lys	Tyr	Trp
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Asp	Tyr	Arg	Tyr	Lys	Lys	Asn	Leu	Lys	Ala	Leu	Tyr	Val	Val	His	Pro
	130					135					140				
Thr	Ser	Phe	Ile	Lys	Val	Leu	Trp	Asn	Ile	Leu	Lys	Pro	Leu	Ile	Ser
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			180					185					190		
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Pro	Pro	Val	Leu	Arg	Phe	Thr	Val	Thr	Tyr	Leu	Arg	Glu	Lys	Gly	Leu
				245					250					255	
Arg	Thr	Glu	Gly	Leu	Phe	Arg	Arg	Ser	Ala	Ser	Val	Gln	Thr	Val	Arg
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Tyr	Gly	Asp	Ile	His	Ile	Pro	Ala	Val	Ile	Leu	Lys	Thr	Phe	Leu	Arg
	290					295					300				
Glu	Leu	Pro	Gln	Pro	Leu	Leu	Thr	Phe	Gln	Ala	Tyr	Glu	Gln	Ile	Leu
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Gly	Ile	Thr	Cys	Val	Glu	Ser	Ser	Leu	Arg	Val	Thr	Gly	Cys	Arg	Gln
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			340					345					350		
Met	Gly	Phe	Leu	His	Ala	Val	Ser	Arg	Glu	Ser	Ile	Phe	Asn	Lys	Met
		355					360					365			
Asn	Ser	Ser	Asn	Leu	Ala	Cys	Val	Phe	Gly	Leu	Asn	Leu	Ile	Trp	Pro
	370					375					380				
Ser	Gln	Gly	Val	Ser	Ser	Leu	Ser	Ala	Leu	Val	Pro	Leu	Asn	Met	Phe
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Thr	Glu	Leu	Leu	Ile	Glu	Tyr	Tyr	Glu	Lys	Ile	Phe	Ser	Thr	Pro	Glu
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			420					425					430		
Ala	Pro	Leu	Gln	Glu	Ala	Val	Pro	Arg	Thr	Gln	Ala	Thr	Gly	Leu	Thr
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Lys	Pro	Thr	Leu	Pro	Pro	Ser	Pro	Leu	Met	Ala	Ala	Arg	Arg	Arg	Leu
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<210> 15

<211> 2043

<212> DNA

<213> Homo sapiens

<400> 15

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<210> 16

<211> 643

<212> PRT

<213> Homo sapiens

<400> 16

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Gln Gln Arg Arg Ala Cys Ala Asn Ala Thr Trp Asn Ser Ile His Asn
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Gly Val Ile Ala Val Phe Gln Arg Lys Gly Leu Pro Asp Gln Glu Leu
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Phe Ser Leu Asn Glu Gly Val Arg Gln Leu Leu Lys Thr Glu Leu Gly
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Ser Phe Phe Thr Glu Tyr Leu Gln Asn Gln Leu Leu Thr Lys Gly Met
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<212> DNA

<213> Homo sapiens

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 Asp Ser Leu Ala Glu Thr Trp Asp Phe Phe Phe Ser Asp Val Leu Pro
 115 120 125
 Met Leu Gln Ala Ile Phe Tyr Pro Val Gln Gly Lys Glu Pro Ser Val
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 Arg Gln Leu Ala Leu Leu His Phe Arg Asn Ala Ile Thr Leu Ser Val
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 Lys Leu Glu Asp Ala Leu Ala Arg Ala His Ala Arg Val Pro Pro Ala
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 Ile Val Gln Met Leu Leu Val Leu Gln Gly Val His Glu Ser Arg Gly
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 Val Thr Glu Asp Tyr Leu Arg Leu Glu Thr Leu Val Gln Lys Val Val
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 Thr His Ser Cys Ile Leu Glu Leu Gln Arg Asp Lys Ala Ala Ala Ala
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 Arg His Gly Ile Leu Gln Val Ala Gly Asp Asp Arg Phe Gly Arg Arg
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 His Gln Arg Leu Leu Glu Tyr Leu Lys Tyr Thr Leu Asp Gln Tyr Val
 305 310 315 320
 Glu Asn Asp Tyr Thr Ile Val Tyr Phe His Tyr Gly Leu Asn Ser Arg
 325 330 335
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 Arg Lys Asp Gly Asp Leu Thr Met Trp Pro Arg Leu Val Ser Asn Ser
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Lys Leu Lys Arg Ser Ser His Leu Ser Leu Pro Lys Tyr Trp Asp Tyr
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 Arg Tyr Lys Lys Asn Leu Lys Ala Leu Tyr Val Val His Pro Thr Ser
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 His Leu Lys Tyr Asp Gln Leu Val Ile Pro Pro Glu Val Leu Arg Tyr
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 Asp Glu Lys Leu Gln Ser Leu His Glu Gly Arg Thr Pro Pro Pro Thr
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 Lys Thr Pro Pro Pro Arg Pro Pro Leu Pro Thr Gln Gln Phe Gly Val
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 Ser Leu Gln Tyr Leu Lys Asp Lys Asn Gln Gly Glu Leu Ile Pro Pro
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 Val Leu Arg Phe Thr Val Thr Tyr Leu Arg Glu Lys Gly Leu Arg Thr
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 Glu Gly Leu Phe Arg Arg Ser Ala Ser Val Gln Thr Val Arg Glu Ile
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 595 600 605
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 625 630 635 640
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 645 650 655
 Leu Leu Ile Glu Tyr Tyr Glu Lys Ile Phe Ser Thr Pro Glu Ala Pro
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 Gly Glu His Gly Leu Ala Pro Trp Glu Gln Gly Ser Arg Ala Ala Pro
 675 680 685
 Leu Gln Glu Ala Val Pro Arg Thr Gln Ala Thr Gly Leu Thr Lys Pro
 690 695 700
 Thr Leu Pro Pro Ser Pro Leu Met Ala Ala Arg Arg Arg Leu Xaa Cys
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<212> PRT

<213> Homo sapiens

<400> 19

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Gly	Val	Ile	Ala	Val	Phe	Gln	Arg	Lys	Gly	Leu	Pro	Asp	Gln	Glu	Leu	50	55	60
Phe	Ser	Leu	Asn	Glu	Gly	Val	Arg	Gln	Leu	Leu	Lys	Thr	Glu	Leu	Gly	65	70	75
Ser	Phe	Phe	Thr	Glu	Tyr	Leu	Gln	Asn	Gln	Leu	Leu	Thr	Lys	Gly	Met	85	90	95
Val	Ile	Leu	Arg	Asp	Lys	Ile	Arg	Phe	Tyr	Glu	Gly	Gln	Lys	Leu	Leu	100	105	110
Asp	Ser	Leu	Ala	Glu	Thr	Trp	Asp	Phe	Phe	Phe	Ser	Asp	Val	Leu	Pro	115	120	125
Met	Leu	Gln	Ala	Ile	Phe	Tyr	Pro	Val	Gln	Gly	Lys	Glu	Pro	Ser	Val	130	135	140
Arg	Gln	Leu	Ala	Leu	Leu	His	Phe	Arg	Asn	Ala	Ile	Thr	Leu	Ser	Val	145	150	155
Lys	Leu	Glu	Asp	Ala	Leu	Ala	Arg	Ala	His	Ala	Arg	Val	Pro	Pro	Ala	165	170	175
Ile	Val	Gln	Met	Leu	Leu	Val	Leu	Gln	Gly	Val	His	Glu	Ser	Arg	Gly	180	185	190
Val	Thr	Glu	Asp	Tyr	Leu	Arg	Leu	Glu	Thr	Leu	Val	Gln	Lys	Val	Val	195	200	205
Ser	Pro	Tyr	Leu	Gly	Thr	Tyr	Gly	Leu	His	Ser	Ser	Glu	Gly	Pro	Phe	210	215	220
Thr	His	Ser	Cys	Ile	Leu	Glu	Leu	Gln	Arg	Asp	Lys	Ala	Ala	Ala	Ala	225	230	235
Ala	Val	Leu	Gly	Ala	Val	Arg	Lys	Arg	Pro	Ser	Val	Val	Pro	Met	Ala	245	250	255
Gly	Gln	Asp	Pro	Ala	Leu	Ser	Thr	Ser	His	Pro	Phe	Tyr	Asp	Val	Ala	260	265	270
Arg	His	Gly	Ile	Leu	Gln	Val	Ala	Gly	Asp	Asp	Arg	Phe	Gly	Arg	Arg	275	280	285
Val	Val	Thr	Phe	Ser	Cys	Cys	Arg	Met	Pro	Pro	Ser	His	Glu	Leu	Asp	290	295	300
His	Gln	Arg	Leu	Leu	Glu	Tyr	Leu	Lys	Tyr	Thr	Leu	Asp	Gln	Tyr	Val	305	310	315
Glu	Asn	Asp	Tyr	Thr	Ile	Val	Tyr	Phe	His	Tyr	Gly	Leu	Asn	Ser	Arg	325	330	335
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Arg	Tyr	Lys	Lys	Asn	Leu	Lys	Ala	Leu	Tyr	Val	Val	His	Pro	Thr	Ser	385	390	395
Phe	Ile	Lys	Val	Leu	Trp	Asn	Ile	Leu	Lys	Pro	Leu	Ile	Ser	His	Lys	405	410	415
Phe	Gly	Lys	Lys	Val	Ile	Tyr	Phe	Asn	Tyr	Leu	Ser	Glu	Leu	His	Glu	420	425	430
His	Leu	Lys	Tyr	Asp	Gln	Leu	Val	Ile	Pro	Pro	Glu	Val	Leu	Arg	Tyr	435	440	445
Asp	Glu	Lys	Leu	Gln	Ser	Leu	His	Glu	Gly	Arg	Thr	Pro	Pro	Pro	Thr	450	455	460
Lys	Thr	Pro	Pro	Pro	Arg	Pro	Pro	Leu	Pro	Thr	Gln	Gln	Phe	Gly	Val	465	470	475
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Ser Leu Gln Tyr Leu Lys Asp Lys Asn Gln Gly Glu Leu Ile Pro Pro
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 Val Leu Arg Phe Thr Val Thr Tyr Leu Arg Glu Lys Gly Leu Arg Thr
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 Glu Gly Leu Phe Arg Arg Ser Ala Ser Val Gln Thr Val Arg Glu Ile
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 Gln Arg Leu Tyr Asn Gln Gly Lys Pro Val Asn Phe Asp Asp Tyr Gly
 530 535 540
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 Pro Gln Pro Leu Leu Thr Phe Gln Ala Tyr Glu Gln Ile Leu Gly Ile
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 595 600 605
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 Gly Val Ser Ser Leu Ser Ala Leu Val Pro Leu Asn Met Phe Thr Glu
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 Leu Leu Ile Glu Tyr Tyr Glu Lys Ile Phe Ser Thr Pro Glu Ala Pro
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 Gly Glu His Gly Leu Ala Pro Trp Glu Gln Gly Ser Arg Ala Ala Pro
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<210> 21
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 <212> PRT
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<400> 21

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Arg	Arg	Val	Val	Thr	Phe	Ser	Cys	Cys	Arg	Met	Pro	Pro	Ser	His	Glu	35	40	45	
Leu	Asp	His	Gln	Arg	Leu	Leu	Asp	Arg	Tyr	Lys	Lys	Asn	Leu	Lys	Ala	50	55	60	
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Asn	Tyr	Leu	Ser	Glu	Leu	His	Glu	His	Leu	Lys	Tyr	Asp	Gln	Leu	Val	100	105	110	
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Ser	Ile	Phe	Asn	Lys	Met	Asn	Ser	Ser	Asn	Leu	Ala	Cys	Val	Phe	Gly	290	295	300	
Leu	Asn	Leu	Ile	Trp	Pro	Ser	Gln	Gly	Val	Ser	Ser	Leu	Ser	Ala	Leu	305	310	315	320
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Ile	Phe	Ser	Thr	Pro	Glu	Ala	Pro	Gly	Glu	His	Gly	Leu	Ala	Pro	Trp	340	345	350	
Glu	Gln	Gly	Ser	Arg	Ala	Ala	Pro	Leu	Gln	Glu	Ala	Val	Pro	Arg	Thr	355	360	365	
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380

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<211> 2019
<212> DNA
<213> Homo sapiens

<400> 22

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<213> Homo sapiens

<400> 23

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35           40           45

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Ser	Phe	Phe	Thr	Glu	Tyr	Leu	Gln	Asn	Gln	Leu	Leu	Thr	Lys	Gly	Met	85	90	95
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Asp	Ser	Leu	Ala	Glu	Thr	Trp	Asp	Phe	Phe	Phe	Ser	Asp	Val	Leu	Pro	115	120	125
Met	Leu	Gln	Ala	Ile	Phe	Tyr	Pro	Val	Gln	Gly	Lys	Glu	Pro	Ser	Val	130	135	140
Arg	Gln	Leu	Ala	Leu	Leu	His	Phe	Arg	Asn	Ala	Ile	Thr	Leu	Ser	Val	145	150	155
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Ala	Val	Leu	Gly	Ala	Val	Arg	Lys	Arg	Pro	Ser	Val	Val	Pro	Met	Ala	245	250	255
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Lys	Thr	Pro	Pro	Pro	Arg	Pro	Pro	Leu	Pro	Thr	Gln	Gln	Phe	Gly	Val	465	470	475
Ser	Leu	Gln	Tyr	Leu	Lys	Asp	Lys	Asn	Gln	Gly	Glu	Leu	Ile	Pro	Pro	485	490	495
Val	Leu	Arg	Phe	Thr	Val	Thr	Tyr	Leu	Arg	Glu	Lys	Gly	Leu	Pro	Glu	500	505	510

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Leu	Asp	His	Gln	Arg	Leu	Leu	Glu	Tyr	Leu	Lys	Tyr	Thr	Leu	Asp	Gln
	50				55						60				
Tyr	Val	Glu	Asn	Asp	Tyr	Thr	Ile	Val	Tyr	Phe	His	Tyr	Gly	Leu	Asn
65				70					75						80
Ser	Arg	Asn	Lys	Pro	Ser	Leu	Gly	Trp	Leu	Gln	Ser	Ala	Tyr	Lys	Glu
				85					90					95	
Phe	Asp	Arg	Lys	Asp	Gly	Asp	Leu	Thr	Met	Trp	Pro	Arg	Leu	Val	Ser
			100					105					110		
Asn	Ser	Lys	Leu	Lys	Arg	Ser	Ser	His	Leu	Ser	Leu	Pro	Lys	Tyr	Trp
		115					120					125			
Asp	Tyr	Arg	Tyr	Lys	Lys	Asn	Leu	Lys	Ala	Leu	Tyr	Val	Val	His	Pro
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Thr	Ser	Phe	Ile	Lys	Val	Leu	Trp	Asn	Ile	Leu	Lys	Pro	Leu	Ile	Ser
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Ser	Leu	Ser	Ala	Leu	Val	Pro	Leu	Asn	Met	Phe	Thr	Glu	Leu	Leu	Ile
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Glu	Tyr	Tyr	Glu	Lys	Ile	Phe	Ser	Thr	Pro	Glu	Ala	Pro	Gly	Glu	His
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<210> 27

<211> 461

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<213> Homo sapiens

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 35              40              45
Gly Val Ile Ala Val Phe Gln Arg Lys Gly Leu Pro Asp Gln Glu Leu
 50              55              60
Phe Ser Leu Asn Glu Gly Val Arg Gln Leu Leu Lys Thr Glu Leu Gly
 65              70              75              80
Ser Phe Phe Thr Glu Tyr Leu Gln Asn Gln Leu Leu Thr Lys Gly Met
 85              90              95
Val Ile Leu Arg Asp Lys Ile Arg Phe Tyr Glu Gly Gln Lys Leu Leu
100              105              110
Asp Ser Leu Ala Glu Thr Trp Asp Phe Phe Phe Ser Asp Val Leu Pro
115              120              125
Met Leu Gln Ala Ile Phe Tyr Pro Val Gln Gly Lys Glu Pro Ser Val
130              135              140
Arg Gln Leu Ala Leu Leu His Phe Arg Asn Ala Ile Thr Leu Ser Val
145              150              155              160
Lys Leu Glu Asp Ala Leu Ala Arg Ala His Ala Arg Val Pro Pro Ala
165              170              175
Ile Val Gln Met Leu Leu Val Leu Gln Gly Val His Glu Ser Arg Gly
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Val Thr Glu Asp Tyr Leu Arg Leu Glu Thr Leu Val Gln Lys Val Val
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Thr	Pro	Pro	Pro	Thr	Lys	Thr	Pro	Pro	Pro	Arg	Pro	Pro	Leu	Pro	Thr
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Gln	Gln	Phe	Gly	Val	Ser	Leu	Gln	Tyr	Leu	Lys	Asp	Lys	Asn	Gln	Gly
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Lys	Ala	Ser	Gln	Ser	Thr	Thr	Thr	Ser	Ser	Ser	Ala	Thr	Ser	Trp	Ala
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<211> 1176

<212> DNA

<213> Homo sapiens

<400> 28

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Lys	Gln	Gln	Tyr	Asp	Glu	Leu	Glu	Ala	Glu	Tyr	Asp	Ser	Leu	Lys	Gln
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Glu	Leu	Glu	Gln	Leu	Lys	Glu	Ala	Phe	Gly	Gln	Ser	Phe	Ser	Ile	His
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Gln	Asn	Glu	Leu	Lys	Gln	Ser	Arg	Ala	Val	Val	Thr	Asn	Val	Gln	Ala
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Glu	Asn	Glu	Arg	Leu	Thr	Ala	Val	Val	Gln	Asp	Leu	Lys	Glu	Asn	Asn
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Glu	Met	Val	Glu	Leu	Gln	Arg	Ile	Arg	Met	Lys	Asp	Glu	Ile	Arg	Glu
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Tyr	Lys	Phe	Arg	Glu	Ala	Arg	Leu	Leu	Gln	Asp	Tyr	Thr	Glu	Leu	Glu
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Glu	Glu	Asn	Ile	Thr	Leu	Gln	Lys	Leu	Val	Ser	Thr	Leu	Lys	Gln	Asn
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Glu	Ile	Ala	Glu	His	Gln	Leu	Glu	Glu	Ala	Leu	Glu	Thr	Leu	Lys	Asn
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				405					410					415	
Glu	Cys	Lys	Tyr	Arg	Val	Ala	Val	Thr	Glu	Val	Ile	Asp	Leu	Lys	Ala
			420					425					430		
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Thr	Asp	Glu	Lys	Ala	Lys	Tyr	Glu	Ser	Lys	Ile	Gln	Met	Tyr	Asp	Glu
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Asp	Gln	Ser	Arg	Pro	Arg	Thr	Ser	Gly	Ala	Ser	Tyr	Leu	Gln	Asn	Leu
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Leu	Arg	Val	Pro	Pro	Asp	Pro	Thr	Ser	Thr	Glu	Ser	Phe	Leu	Leu	Lys
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<210> 39

<211> 790

<212> PRT

<213> Homo sapiens

<400> 39

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Glu Tyr Thr Gly Ser Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp
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Gln Asp Arg Gly Asp Gly Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly
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Phe Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr
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Lys Glu Val Tyr Thr Ala Thr Val Pro Glu Met Ser Asp Val Gly Thr
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Phe Val Val Gln Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly
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 Arg Arg Asp Ile Val Pro Glu Ala Leu Phe Leu Pro Arg Arg Thr Pro
 690 695 700
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 Lys Glu Asn Asp Thr Asp Pro Thr Ala Pro Pro Tyr Asp Ser Leu Ala
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 Thr Tyr Ala Tyr Glu Gly Thr Gly Ser Val Ala Asp Ser Leu Ser Ser
 740 745 750
 Leu Glu Ser Val Thr Thr Asp Ala Asp Gln Asp Tyr Asp Tyr Leu Ser
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 <211> 987
 <212> DNA
 <213> Homo sapiens

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 <211> 156
 <212> PRT
 <213> Homo sapiens

<400> 41
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 Ile Gln Val Met Met Met Gly Ser Ala Arg Val Ala Glu Leu Leu Leu
 50 55 60
 Leu His Gly Ala Glu Pro Asn Cys Ala Asp Pro Ala Thr Leu Thr Arg
 65 70 75 80

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Tyr	Leu	Arg	Ala	Ala	Ala	Gly	Gly	Thr	Arg	Gly	Ser	Asn	His	Ala	Arg
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<210> 42

<211> 5142

<212> DNA

<213> Homo sapiens

<400> 42

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<210> 43
 <211> 1203
 <212> PRT
 <213> Homo sapiens

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Leu	Arg	Arg	Ser	Met	Gln	Asp	Ala	Thr	Gln	Asp	His	Ala	Val	Leu	Glu		
	530					535					540						
Ala	Glu	Arg	Gln	Lys	Met	Ser	Ala	Leu	Val	Arg	Gly	Leu	Gln	Arg	Glu		
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Leu	Glu	Glu	Thr	Ser	Glu	Glu	Thr	Gly	His	Trp	Gln	Ser	Met	Phe	Gln		
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Lys	Asn	Lys	Glu	Asp	Leu	Arg	Ala	Thr	Lys	Gln	Glu	Leu	Leu	Gln	Leu		
			580					585					590				
Arg	Met	Glu	Lys	Glu	Glu	Met	Glu	Glu	Glu	Leu	Gly	Glu	Lys	Ile	Glu		
	595						600					605					
Val	Leu	Gln	Arg	Glu	Leu	Glu	Gln	Ala	Arg	Ala	Ser	Ala	Gly	Asp	Thr		
	610						615					620					
Arg	Gln	Val	Glu	Val	Leu	Lys	Lys	Glu	Leu	Leu	Arg	Thr	Gln	Glu	Glu		
625					630					635					640		
Leu	Lys	Glu	Leu	Gln	Ala	Glu	Arg	Gln	Ser	Gln	Glu	Val	Ala	Gly	Arg		
				645					650						655		
His	Arg	Asp	Arg	Glu	Leu	Glu	Lys	Gln	Leu	Ala	Val	Leu	Arg	Val	Glu		
			660					665					670				
Ala	Asp	Arg	Gly	Arg	Glu	Leu	Glu	Glu	Gln	Asn	Leu	Gln	Leu	Gln	Lys		
	675						680					685					
Thr	Leu	Gln	Gln	Leu	Arg	Gln	Asp	Cys	Glu	Glu	Ala	Ser	Lys	Ala	Lys		
	690					695					700						
Met	Val	Ala	Glu	Ala	Glu	Ala	Thr	Val	Leu	Gly	Gln	Arg	Arg	Ala	Ala		
705					710					715					720		
Val	Glu	Thr	Thr	Leu	Arg	Glu	Thr	Gln	Glu	Asn	Asp	Glu	Phe	Arg			
				725					730					735			
Arg	Arg	Ile	Leu	Gly	Leu	Glu	Gln	Gln	Leu	Lys	Glu	Thr	Arg	Gly	Leu		
			740					745					750				
Val	Asp	Gly	Gly	Glu	Ala	Val	Glu	Ala	Arg	Leu	Arg	Asp	Lys	Leu	Gln		
	755						760					765					
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Gln	Thr	Leu	Asn	Arg	Ala	Leu	Glu	Glu	Glu	Gly	Lys	Gln	Arg	Glu	Val		
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Leu	Arg	Arg	Gly	Lys	Ala	Glu	Leu	Glu	Glu	Gln	Lys	Arg	Leu	Leu	Asp		
	835						840					845					
Arg	Thr	Val	Asp	Arg	Leu	Asn	Lys	Glu	Leu	Glu	Lys	Ile	Gly	Glu	Asp		
	850					855					860						
Ser	Lys	Gln	Ala	Leu	Gln	Leu	Gln	Ala	Gln	Leu	Glu	Asp	Tyr	Lys			
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Glu	Lys	Ala	Arg	Arg	Glu	Val	Ala	Asp	Ala	Gln	Arg	Gln	Ala	Lys	Asp		
				885					890					895			
Trp	Ala	Ser	Glu	Ala	Glu	Lys	Thr	Ser	Gly	Gly	Leu	Ser	Arg	Leu	Gln		
			900					905					910				
Asp	Glu	Ile	Gln	Arg	Leu	Arg	Gln	Ala	Leu	Gln	Ala	Ser	Gln	Ala	Glu		
	915						920					925					
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	930					935					940						
Gly	Leu	Glu	Gln	Glu	Ala	Glu	Asn	Lys	Lys	Arg	Ser	Gln	Asp	Asp	Arg		
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<210> 44
<211> 1925
<212> DNA
<213> Homo sapiens
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gccaatataa	gcaacgatca	catcgacacc	tgggagtgga	atgatgtgac	gctctacggc	360
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gccgaattta	taaaggaagc	ccagccagg	aaaaagcagc	tcctgctcag	cgcagcactg	660
tctgcgggga	aggtcaccat	tgacagcagc	tatgacattg	ccaagataac	ccaacacctg	720
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atctgtgact	tctctcgcgg	agccacagtc	catagaacct	tcggccagca	ggtcccctat	1080
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cgctttgctt tgggtctatct ttgagcgccc actagacca ctggactcac ctcccccatc 1860
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atggtt                                     1925

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<210> 45

<211> 383

<212> PRT

<213> Homo sapiens

<400> 45

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 20          25          30
Gln Tyr Arg Glu Gly Asp Gly Ser Cys Phe Pro Asp Ala Leu Asp Arg
 35          40          45
Phe Leu Cys Thr His Ile Ile Tyr Ser Phe Ala Asn Ile Ser Asn Asp
 50          55          60
His Ile Asp Thr Trp Glu Trp Asn Asp Val Thr Leu Tyr Gly Met Leu
 65          70          75          80
Asn Thr Leu Lys Asn Arg Asn Pro Asn Leu Lys Thr Leu Leu Ser Val
 85          90          95
Gly Gly Trp Asn Phe Gly Ser Gln Arg Phe Ser Lys Ile Ala Ser Asn
100          105          110
Thr Gln Ser Arg Arg Thr Phe Ile Lys Ser Val Pro Pro Phe Leu Arg
115          120          125
Thr His Gly Phe Asp Gly Leu Asp Leu Ala Trp Leu Tyr Pro Gly Arg
130          135          140
Arg Asp Lys Gln His Phe Thr Thr Leu Ile Lys Glu Met Lys Ala Glu
145          150          155          160
Phe Ile Lys Glu Ala Gln Pro Gly Lys Lys Gln Leu Leu Leu Ser Ala
165          170          175
Ala Leu Ser Ala Gly Lys Val Thr Ile Asp Ser Ser Tyr Asp Ile Ala
180          185          190
Lys Ile Ser Gln His Leu Asp Phe Ile Ser Ile Met Thr Tyr Asp Phe
195          200          205
His Gly Ala Trp Arg Gly Thr Thr Gly His His Ser Pro Leu Phe Arg
210          215          220
Gly Gln Glu Asp Ala Ser Pro Asp Arg Phe Ser Asn Thr Asp Tyr Ala
225          230          235          240
Val Gly Tyr Met Leu Arg Leu Gly Ala Pro Ala Ser Lys Leu Val Met
245          250          255
Gly Ile Pro Thr Phe Gly Arg Ser Phe Thr Leu Ala Ser Ser Glu Thr
260          265          270
Gly Val Gly Ala Pro Ile Ser Gly Pro Gly Ile Pro Gly Arg Phe Thr
275          280          285
Lys Glu Ala Gly Thr Leu Ala Tyr Tyr Glu Ile Cys Asp Phe Leu Arg

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55

290		295		300
Gly Ala Thr Val His Arg Thr Leu Gly Gln Gln Val Pro Tyr Ala Thr				
305		310		315
Lys Gly Asn Gln Trp Val Gly Tyr Asp Asp Gln Glu Ser Val Lys Ser				
		325		330
Lys Val Gln Tyr Leu Lys Asp Arg Gln Leu Ala Gly Ala Met Val Trp				
		340		345
Ala Leu Asp Leu Asp Asp Phe Gln Gly Ser Phe Cys Gly Gln Asp Leu				
		355		360
Arg Phe Pro Leu Thr Asn Ala Ile Lys Asp Ala Leu Ala Ala Thr				
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<210> 46
 <211> 1528
 <212> DNA
 <213> Homo sapiens

<400> 46

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ccaagagcga cacaatggat atgaccccg gacaatgaag cacaccacgg atctagatgc 600
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<210> 47
 <211> 417
 <212> PRT
 <213> Homo sapiens

<400> 47

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Leu Leu Ala Leu Ala Gly Ala Gly Ser Leu Ala Ala Gly Phe Leu Leu
20 25 30
Arg Pro Glu Pro Val Arg Ala Ala Ser Glu Arg Arg Arg Leu Tyr Pro
35 40 45

Pro Ser Ala Glu Tyr Pro Asp Leu Arg Lys His Asn Asn Cys Met Ala
 50 55 60
 Ser His Leu Thr Pro Ala Val Tyr Ala Arg Leu Cys Asp Lys Thr Thr
 65 70 75 80
 Pro Thr Gly Trp Thr Leu Asp Gln Cys Ile Gln Thr Gly Val Asp Asn
 85 90 95
 Pro Gly His Pro Phe Ile Lys Thr Val Gly Met Val Ala Gly Asp Glu
 100 105 110
 Glu Thr Tyr Glu Val Phe Ala Asp Leu Phe Asp Pro Val Ile Gln Glu
 115 120 125
 Arg His Asn Gly Tyr Asp Pro Arg Thr Met Lys His Thr Thr Asp Leu
 130 135 140
 Asp Ala Ser Lys Ile Arg Ser Gly Tyr Phe Asp Glu Arg Tyr Val Leu
 145 150 155 160
 Ser Ser Arg Val Arg Thr Gly Arg Ser Ile Arg Gly Leu Ser Leu Pro
 165 170 175
 Pro Ala Cys Thr Arg Ala Glu Arg Arg Glu Val Glu Arg Val Val Val
 180 185 190
 Asp Ala Leu Ser Gly Leu Lys Gly Asp Leu Ala Gly Arg Tyr Tyr Arg
 195 200 205
 Leu Ser Glu Met Thr Glu Ala Glu Gln Gln Gln Leu Ile Asp Asp His
 210 215 220
 Phe Leu Phe Asp Lys Pro Val Ser Pro Leu Leu Thr Ala Ala Gly Met
 225 230 235 240
 Ala Arg Asp Trp Pro Asp Ala Arg Gly Ile Trp His Asn Asn Glu Lys
 245 250 255
 Ser Phe Leu Ile Trp Val Asn Glu Glu Asp His Thr Arg Val Ile Ser
 260 265 270
 Met Glu Lys Gly Gly Asn Met Lys Arg Val Phe Glu Arg Phe Cys Arg
 275 280 285
 Gly Leu Lys Glu Val Glu Arg Leu Ile Gln Glu Arg Gly Trp Glu Phe
 290 295 300
 Met Trp Asn Glu Arg Leu Gly Tyr Ile Leu Thr Cys Pro Ser Asn Leu
 305 310 315 320
 Gly Thr Gly Leu Arg Ala Gly Val His Ile Lys Leu Pro Leu Leu Ser
 325 330 335
 Lys Asp Ser Arg Phe Pro Lys Ile Leu Glu Asn Leu Arg Leu Gln Lys
 340 345 350
 Arg Gly Thr Gly Gly Val Asp Thr Ala Ala Thr Gly Gly Val Phe Asp
 355 360 365
 Ile Ser Asn Leu Asp Arg Leu Gly Lys Ser Glu Val Glu Leu Val Gln
 370 375 380
 Leu Val Ile Asp Gly Val Asn Tyr Leu Ile Asp Cys Glu Arg Arg Leu
 385 390 395 400
 Glu Arg Gly Gln Asp Ile Arg Ile Pro Thr Pro Val Ile His Thr Lys
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<210> 48

<211> 2365

<212> DNA

<213> Homo sapiens

<400> 48

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<210> 49

<211> 228

<212> PRT

<213> Homo sapiens

<400> 49

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 20             25             30
Ser Thr Ile Asp Gly Thr Val Ile Thr Thr Ala Thr Tyr Trp Ala Asn
 35             40             45
Leu Trp Lys Ala Cys Val Thr Asp Ser Thr Gly Val Ser Asn Cys Lys
 50             55             60
Asp Phe Pro Ser Met Leu Ala Leu Asp Gly Tyr Ile Gln Ala Cys Arg
 65             70             75             80
Gly Leu Met Ile Ala Ala Val Ser Leu Gly Phe Phe Gly Ser Ile Phe
 85             90             95
Ala Leu Phe Gly Met Lys Cys Thr Lys Val Gly Gly Ser Asp Lys Ala

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			100					105					110				
Lys	Ala	Lys	Ile	Ala	Cys	Leu	Ala	Gly	Ile	Val	Phe	Ile	Leu	Ser	Gly		
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Leu	Cys	Ser	Met	Thr	Gly	Cys	Ser	Leu	Tyr	Ala	Asn	Lys	Ile	Thr	Thr		
	130					135						140					
Glu	Phe	Phe	Asp	Pro	Leu	Phe	Val	Glu	Gln	Lys	Tyr	Glu	Leu	Gly	Ala		
145					150					155					160		
Ala	Leu	Phe	Ile	Gly	Trp	Ala	Gly	Ala	Ser	Leu	Cys	Ile	Ile	Gly	Gly		
			165					170						175			
Val	Ile	Phe	Cys	Phe	Ser	Ile	Ser	Asp	Asn	Asn	Lys	Thr	Pro	Arg	Tyr		
			180					185					190				
Thr	Tyr	Asn	Gly	Ala	Thr	Ser	Val	Met	Ser	Ser	Arg	Thr	Lys	Tyr	His		
		195					200					205					
Gly	Gly	Glu	Asp	Phe	Lys	Thr	Thr	Asn	Pro	Ser	Lys	Gln	Phe	Asp	Lys		
	210					215					220						
Asn	Ala	Tyr	Val														
225																	

<210> 50
 <211> 1024
 <212> DNA
 <213> Homo sapiens

<400> 50
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 gcaactcaag acacctgcag cagggcgtga gaaaaagtaa aagaccagta ttttcacatt 180
 gccaggtaac agaaacacag aagactgaca cccgccactt aagtggggcc agggctggtg 240
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 tcgcttgctt ctttgccctt ttctctgctg gggtttttgat tgtggccacc tggactgact 360
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 cagccgcggg tgtttccatg gccaagtcat actcagcccc tcgcacagag acggccaaaa 960
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 aatc 1024

<210> 51
 <211> 305
 <212> PRT
 <213> Homo sapiens

<400> 51
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 Pro Val Phe Ser His Cys Gln Val Pro Glu Thr Gln Lys Thr Asp Thr
 35 40 45
 Arg His Leu Ser Gly Ala Arg Ala Gly Val Cys Pro Cys Cys His Pro
 50 55 60

Asp Gly Leu Leu Ala Thr Met Arg Asp Leu Leu Gln Tyr Ile Ala Cys
 65 70 75 80
 Phe Phe Ala Phe Phe Ser Ala Gly Phe Leu Ile Val Ala Thr Trp Thr
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 <212> DNA
 <213> Homo sapiens

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 <213> Homo sapiens

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Thr	Glu	His	Ser	Asn	Ile	Tyr	Leu	Gln	Asn	Gly	Pro	Asp	Arg	Ile	Gly
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Arg	Thr	Thr	Ile	Glu	Lys	Pro	Val	Trp	Leu	Gly	Phe	Leu	Gly	Pro	Ile
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Glu	Glu	Glu	His	Leu	Gly	Ile	Leu	Gly	Pro	Gln	Leu	His	Ala	Asp	Val		
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Ile Asn Gly Arg Met Phe Gly Asn Leu Gln Gly Leu Thr Met His Val						
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	980		985		990	
Leu His Thr Val His Phe His Gly His Ser Phe Gln Tyr Lys His Arg						
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Thr Leu Glu Met Phe Pro Arg Thr Pro Gly Ile Trp Leu Leu His Cys						
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<210> 57
 <211> 852
 <212> PRT
 <213> Homo sapiens

<400> 57

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Asn	Glu	Asp	Phe	Gln	Glu	Ser	Asn	Arg	Met	Tyr	Ser	Val	Asn	Gly	Tyr
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Thr	Phe	Gly	Ser	Leu	Pro	Gly	Leu	Ser	Met	Cys	Ala	Glu	Asp	Arg	Val
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Lys	Trp	Tyr	Leu	Phe	Gly	Met	Gly	Asn	Glu	Val	Asp	Val	His	Ala	Ala
					70					75					80
Phe	Phe	His	Gly	Gln	Ala	Leu	Thr	Asn	Lys	Asn	Tyr	Arg	Ile	Asp	Thr
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Ile	Asn	Leu	Phe	Pro	Ala	Thr	Leu	Phe	Asp	Ala	Tyr	Met	Val	Ala	Gln
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Asn	Pro	Gly	Glu	Trp	Met	Leu	Ser	Cys	Gln	Asn	Leu	Asn	His	Leu	Lys
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Ala	Gly	Leu	Gln	Ala	Phe	Phe	Gln	Val	Gln	Glu	Cys	Asn	Lys	Ser	Ser
	130					135					140				
Ser	Lys	Asp	Asn	Ile	Arg	Gly	Lys	His	Val	Arg	His	Tyr	Tyr	Ile	Ala
					150					155					160
Ala	Glu	Glu	Ile	Ile	Trp	Asn	Tyr	Ala	Pro	Ser	Gly	Ile	Asp	Ile	Phe
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Thr	Lys	Glu	Asn	Leu	Thr	Ala	Pro	Gly	Ser	Asp	Ser	Ala	Val	Phe	Phe
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Glu	Gln	Gly	Thr	Thr	Arg	Ile	Gly	Gly	Ser	Tyr	Lys	Lys	Leu	Val	Tyr
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Arg	Glu	Tyr	Thr	Asp	Ala	Ser	Phe	Thr	Asn	Arg	Lys	Glu	Arg	Gly	Pro
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Glu	Glu	Glu	His	Leu	Gly	Ile	Leu	Gly	Pro	Val	Ile	Trp	Ala	Glu	Val

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Gly Asp Thr Ile Arg Val Thr Phe His Asn Lys Gly Ala Tyr Pro Leu						
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Ser Ile Glu Pro Ile Gly Val Arg Phe Asn Lys Asn Asn Glu Gly Thr						
	260		265		270	
Tyr Tyr Ser Pro Asn Tyr Asn Pro Gln Ser Arg Ser Val Pro Pro Ser						
	275		280		285	
Ala Ser His Val Ala Pro Thr Glu Thr Phe Thr Tyr Glu Trp Thr Val						
	290		295		300	
Pro Lys Glu Val Gly Pro Thr Asn Ala Asp Pro Val Cys Leu Ala Lys						
305		310		315		320
Met Tyr Tyr Ser Ala Val Asp Pro Thr Lys Asp Ile Phe Thr Gly Leu						
	325		330		335	
Ile Gly Pro Met Lys Ile Cys Lys Lys Gly Ser Leu His Ala Asn Gly						
	340		345		350	
Arg Gln Lys Asp Val Asp Lys Glu Phe Tyr Leu Phe Pro Thr Val Phe						
	355		360		365	
Asp Glu Asn Glu Ser Leu Leu Glu Asp Asn Ile Arg Met Phe Thr						
	370		375		380	
Thr Ala Pro Asp Gln Val Asp Lys Glu Asp Glu Asp Phe Gln Glu Ser						
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Asn Lys Met His Ser Met Asn Gly Phe Met Tyr Gly Asn Gln Pro Gly						
	405		410		415	
Leu Thr Met Cys Lys Gly Asp Ser Val Val Trp Tyr Leu Phe Ser Ala						
	420		425		430	
Gly Asn Glu Ala Asp Val His Gly Ile Tyr Phe Ser Gly Asn Thr Tyr						
	435		440		445	
Leu Trp Arg Gly Glu Arg Arg Asp Thr Ala Asn Leu Phe Pro Gln Thr						
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Ser Leu Thr Leu His Met Trp Pro Asp Thr Glu Gly Thr Phe Asn Val						
465		470		475		480
Glu Cys Leu Thr Thr Asp His Tyr Thr Gly Gly Met Lys Gln Lys Tyr						
	485		490		495	
Thr Val Asn Gln Cys Arg Arg Gln Ser Glu Asp Ser Thr Phe Tyr Leu						
	500		505		510	
Gly Glu Arg Thr Tyr Tyr Ile Ala Val Glu Val Glu Trp Asp Tyr						
	515		520		525	
Ser Pro Gln Arg Glu Trp Glu Lys Glu Leu His His Leu Gln Glu Gln						
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Asn Val Ser Asn Ala Phe Leu Asp Lys Gly Glu Phe Tyr Ile Gly Ser						
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Lys Tyr Lys Lys Val Val Tyr Arg Gln Tyr Thr Asp Ser Thr Phe Arg						
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Pro Gln Leu His Ala Asp Val Gly Asp Lys Val Lys Ile Ile Phe Lys						
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Glu Ser Ser Thr Val Thr Pro Thr Leu Pro Gly Glu Thr Leu Thr Tyr						
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Val Trp Lys Ile Pro Glu Arg Ser Gly Ala Gly Thr Glu Asp Ser Ala						
	645		650		655	
Cys Ile Pro Trp Ala Tyr Tyr Ser Thr Val Asp Gln Val Lys Asp Leu						
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Tyr Ser Gly Leu Ile Gly Pro Leu Ile Val Cys Arg Arg Pro Tyr Leu						
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Lys Val Phe Asn Pro Arg Arg Lys Leu Glu Phe Ala Leu Leu Phe Leu						

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Tyr Ser Asp His Pro Glu Lys Val Asn Lys Asp Asp Glu Glu Phe Ile		720
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Glu Ser Asn Lys Met His Ala Ile Asn Gly Arg Met Phe Gly Asn Leu		
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		750
Gln Gly Leu Thr Met His Val Gly Asp Glu Val Asn Trp Tyr Leu Met		
	755	760
		765
Gly Met Gly Asn Glu Ile Asp Leu His Thr Val His Phe His Gly His		
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		780
Ser Phe Gln Tyr Lys His Arg Gly Val Tyr Ser Ser Asp Val Phe Asp		
785	790	795
		800
Ile Phe Pro Gly Thr Tyr Gln Thr Leu Glu Met Phe Pro Arg Thr Pro		
	805	810
		815
Gly Ile Trp Leu Leu His Cys His Val Thr Asp His Ile His Ala Gly		
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 <212> DNA
 <213> Homo sapiens

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<210> 59

<211> 1065

<212> PRT

<213> Homo sapiens

<400> 59

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Trp Asp Tyr Ala Ser Asp His Gly Glu Lys Lys Leu Ile Ser Val Asp
      35           40           45
Thr Glu His Ser Asn Ile Tyr Leu Gln Asn Gly Pro Asp Arg Ile Gly
      50           55           60
Arg Leu Tyr Lys Lys Ala Leu Tyr Leu Gln Tyr Thr Asp Glu Thr Phe
      65           70           75           80
Arg Thr Thr Ile Glu Lys Pro Val Trp Leu Gly Phe Leu Gly Pro Ile
      85           90           95
Ile Lys Ala Glu Thr Gly Asp Lys Val Tyr Val His Leu Lys Asn Leu
      100          105          110
Ala Ser Arg Pro Tyr Thr Phe His Ser His Gly Ile Thr Tyr Tyr Lys
      115          120          125
Glu His Glu Gly Ala Ile Tyr Pro Asp Asn Thr Thr Asp Phe Gln Arg
      130          135          140
Ala Asp Asp Lys Val Tyr Pro Gly Glu Gln Tyr Thr Tyr Met Leu Leu
      145          150          155          160
Ala Thr Glu Glu Gln Ser Pro Gly Glu Gly Asp Gly Asn Cys Val Thr
      165          170          175
Arg Ile Tyr His Ser His Ile Asp Ala Pro Lys Asp Ile Ala Ser Gly
      180          185          190

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Leu	Ile	Gly	Pro	Leu	Ile	Ile	Cys	Lys	Lys	Asp	Ser	Leu	Asp	Lys	Glu	195	200	205
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Asp	Glu	Asn	Phe	Ser	Trp	Tyr	Leu	Glu	Asp	Asn	Ile	Lys	Thr	Tyr	Cys	225	230	235
Ser	Glu	Pro	Glu	Lys	Val	Asp	Lys	Asp	Asn	Glu	Asp	Phe	Gln	Glu	Ser	245	250	255
Asn	Arg	Met	Tyr	Ser	Val	Asn	Gly	Tyr	Thr	Phe	Gly	Ser	Leu	Pro	Gly	260	265	270
Leu	Ser	Met	Cys	Ala	Glu	Asp	Arg	Val	Lys	Trp	Tyr	Leu	Phe	Gly	Met	275	280	285
Gly	Asn	Glu	Val	Asp	Val	His	Ala	Ala	Phe	Phe	His	Gly	Gln	Ala	Leu	290	295	300
Thr	Asn	Lys	Asn	Tyr	Arg	Ile	Asp	Thr	Ile	Asn	Leu	Phe	Pro	Ala	Thr	305	310	315
Leu	Phe	Asp	Ala	Tyr	Met	Val	Ala	Gln	Asn	Pro	Gly	Glu	Trp	Met	Leu	325	330	335
Ser	Cys	Gln	Asn	Leu	Asn	His	Leu	Lys	Ala	Gly	Leu	Gln	Ala	Phe	Phe	340	345	350
Gln	Val	Gln	Glu	Cys	Asn	Lys	Ser	Ser	Ser	Lys	Asp	Asn	Ile	Arg	Gly	355	360	365
Lys	His	Val	Arg	His	Tyr	Tyr	Ile	Ala	Ala	Glu	Glu	Ile	Ile	Trp	Asn	370	375	380
Tyr	Ala	Pro	Ser	Gly	Ile	Asp	Ile	Phe	Thr	Lys	Glu	Asn	Leu	Thr	Ala	385	390	395
Pro	Gly	Ser	Asp	Ser	Ala	Val	Phe	Phe	Glu	Gln	Gly	Thr	Thr	Arg	Ile	405	410	415
Gly	Gly	Ser	Tyr	Lys	Lys	Leu	Val	Tyr	Arg	Glu	Tyr	Thr	Asp	Ala	Ser	420	425	430
Phe	Thr	Asn	Arg	Lys	Glu	Arg	Gly	Pro	Glu	Glu	Glu	His	Leu	Gly	Ile	435	440	445
Leu	Gly	Pro	Val	Ile	Trp	Ala	Glu	Val	Gly	Asp	Thr	Ile	Arg	Val	Thr	450	455	460
Phe	His	Asn	Lys	Gly	Ala	Tyr	Pro	Leu	Ser	Ile	Glu	Pro	Ile	Gly	Val	465	470	475
Arg	Phe	Asn	Lys	Asn	Asn	Glu	Gly	Thr	Tyr	Tyr	Ser	Pro	Asn	Tyr	Asn	485	490	495
Pro	Gln	Ser	Arg	Ser	Val	Pro	Pro	Ser	Ala	Ser	His	Val	Ala	Pro	Thr	500	505	510
Glu	Thr	Phe	Thr	Tyr	Glu	Trp	Thr	Val	Pro	Lys	Glu	Val	Gly	Pro	Thr	515	520	525
Asn	Ala	Asp	Pro	Val	Cys	Leu	Ala	Lys	Met	Tyr	Tyr	Ser	Ala	Val	Asp	530	535	540
Pro	Thr	Lys	Asp	Ile	Phe	Thr	Gly	Leu	Ile	Gly	Pro	Met	Lys	Ile	Cys	545	550	555
Lys	Lys	Gly	Ser	Leu	His	Ala	Asn	Gly	Arg	Gln	Lys	Asp	Val	Asp	Lys	565	570	575
Glu	Phe	Tyr	Leu	Phe	Pro	Thr	Val	Phe	Asp	Glu	Asn	Glu	Ser	Leu	Leu	580	585	590
Leu	Glu	Asp	Asn	Ile	Arg	Met	Phe	Thr	Thr	Ala	Pro	Asp	Gln	Val	Asp	595	600	605
Lys	Glu	Asp	Glu	Asp	Phe	Gln	Glu	Ser	Asn	Lys	Met	His	Ser	Met	Asn	610	615	620
Gly	Phe	Met	Tyr	Gly	Asn	Gln	Pro	Gly	Leu	Thr	Met	Cys	Lys	Gly	Asp	625	630	635
Ser	Val	Val	Trp	Tyr	Leu	Phe	Ser	Ala	Gly	Asn	Glu	Ala	Asp	Val	His	645	650	655

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Pro	Asp	Thr	Glu	Gly	Thr	Phe	Asn	Val	Glu	Cys	Leu	Thr	Thr	Asp	His		
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Tyr	Thr	Gly	Gly	Met	Lys	Gln	Lys	Tyr	Thr	Val	Asn	Gln	Cys	Arg	Arg		
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Ser	Thr	Val	Asp	Gln	Val	Lys	Asp	Leu	Tyr	Ser	Gly	Leu	Ile	Gly	Pro		
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Leu	Ile	Val	Cys	Arg	Arg	Pro	Tyr	Leu	Lys	Val	Phe	Asn	Pro	Arg	Arg		
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Lys	Leu	Glu	Phe	Ala	Leu	Leu	Phe	Leu	Val	Phe	Asp	Glu	Asn	Glu	Ser		
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Trp	Tyr	Leu	Asp	Asp	Asn	Ile	Lys	Thr	Tyr	Ser	Asp	His	Pro	Glu	Lys		
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Val	Asn	Lys	Asp	Asp	Glu	Glu	Phe	Ile	Glu	Ser	Asn	Lys	Met	His	Ala		
945				950						955					960		
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			965						970					975			
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		980					985					990					
Leu	His	Thr	Val	His	Phe	His	Gly	His	Ser	Phe	Gln	Tyr	Lys	His	Arg		
	995					1000						1005					
Gly	Val	Tyr	Ser	Ser	Asp	Val	Phe	Asp	Ile	Phe	Pro	Gly	Thr	Tyr	Gln		
	1010					1015					1020						
Thr	Leu	Glu	Met	Phe	Pro	Arg	Thr	Pro	Gly	Ile	Trp	Leu	Leu	His	Cys		
1025				1030						1035					1040		
His	Val	Thr	Asp	His	Ile	His	Ala	Gly	Met	Glu	Thr	Thr	Tyr	Thr	Val		
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<210> 60

<211> 3881

<212> DNA

<213> Homo sapiens

<220>

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<400> 60

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<210> 61

<211> 1090

<212> PRT

<213> Homo sapiens

<400> 61

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      20             25             30
Trp Asp Tyr Ala Ser Asp His Gly Glu Lys Lys Leu Ile Ser Val Asp
      35             40             45
Thr Glu His Ser Asn Ile Tyr Leu Gln Asn Gly Pro Asp Arg Ile Gly
      50             55             60
Arg Leu Tyr Lys Lys Ala Leu Tyr Leu Gln Tyr Thr Asp Glu Thr Phe
      65             70             75             80
Arg Thr Thr Ile Glu Lys Pro Val Trp Leu Gly Phe Leu Gly Pro Ile
      85             90             95
Ile Lys Ala Glu Thr Gly Asp Lys Val Tyr Val His Leu Lys Asn Leu
      100            105            110
Ala Ser Arg Pro Tyr Thr Phe His Ser His Gly Ile Thr Tyr Tyr Lys
      115            120            125
Glu His Glu Gly Ala Ile Tyr Pro Asp Asn Thr Thr Asp Phe Gln Arg
      130            135            140
Ala Asp Asp Lys Val Tyr Pro Gly Glu Gln Tyr Thr Tyr Met Leu Leu
      145            150            155            160
Ala Thr Glu Glu Gln Ser Pro Gly Glu Gly Asp Gly Asn Cys Val Thr
      165            170            175
Arg Ile Tyr His Ser His Ile Asp Ala Pro Lys Asp Ile Ala Ser Gly
      180            185            190
Leu Ile Gly Pro Leu Ile Ile Cys Lys Lys Asp Ser Leu Asp Lys Glu
      195            200            205
Lys Glu Lys His Ile Asp Arg Glu Phe Val Val Met Phe Ser Val Val
      210            215            220
Asp Glu Asn Phe Ser Trp Tyr Leu Glu Asp Asn Ile Lys Thr Tyr Cys
      225            230            235            240
Ser Glu Pro Glu Lys Val Asp Lys Asp Asn Glu Asp Phe Gln Glu Ser
      245            250            255
Asn Arg Met Tyr Ser Val Asn Gly Tyr Thr Phe Gly Ser Leu Pro Gly
      260            265            270
Leu Ser Met Cys Ala Glu Asp Arg Val Lys Trp Tyr Leu Phe Gly Met
      275            280            285
Gly Asn Glu Val Asp Val His Ala Ala Phe Phe His Gly Gln Ala Leu

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290	295	300
Thr Asn Lys Asn Tyr Arg Ile Asp Thr Ile Asn Leu Phe Pro Ala Thr		
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Leu Phe Asp Ala Tyr Met Val Ala Gln Asn Pro Gly Glu Trp Met Leu		320
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Ser Cys Gln Asn Leu Asn His Leu Lys Ala Gly Leu Gln Ala Phe Phe		335
	340	345
Gln Val Gln Glu Cys Asn Lys Ser Ser Ser Lys Asp Asn Ile Arg Gly		350
	355	360
Lys His Val Arg His Tyr Tyr Ile Ala Ala Glu Glu Ile Ile Trp Asn		365
	370	375
Tyr Ala Pro Ser Gly Ile Asp Ile Phe Thr Lys Glu Asn Leu Thr Ala		380
385	390	395
Pro Gly Ser Asp Ser Ala Val Phe Phe Glu Gln Gly Thr Thr Arg Ile		400
	405	410
Gly Gly Ser Tyr Lys Lys Leu Val Tyr Arg Glu Tyr Thr Asp Ala Ser		415
	420	425
Phe Thr Asn Arg Lys Glu Arg Gly Pro Glu Glu Glu His Leu Gly Ile		430
	435	440
Leu Gly Pro Val Ile Trp Ala Glu Val Gly Asp Thr Ile Arg Val Thr		445
	450	455
Phe His Asn Lys Gly Ala Tyr Pro Leu Ser Ile Glu Pro Ile Gly Val		460
465	470	475
Arg Phe Asn Lys Asn Asn Glu Gly Thr Tyr Tyr Ser Pro Asn Tyr Asn		480
	485	490
Pro Gln Ser Arg Ser Val Pro Pro Ser Ala Ser His Val Ala Pro Thr		495
	500	505
Glu Thr Phe Thr Tyr Glu Trp Thr Val Pro Lys Glu Val Gly Pro Thr		510
	515	520
Asn Ala Asp Pro Val Cys Leu Ala Lys Met Tyr Tyr Ser Ala Val Asp		525
	530	535
Pro Thr Lys Asp Ile Phe Thr Gly Leu Ile Gly Pro Met Lys Ile Cys		540
545	550	555
Lys Lys Gly Ser Leu His Ala Asn Gly Arg Gln Lys Asp Val Asp Lys		560
	565	570
Glu Phe Tyr Leu Phe Pro Thr Val Phe Asp Glu Asn Glu Ser Leu Leu		575
	580	585
Leu Glu Asp Asn Ile Arg Met Phe Thr Thr Ala Pro Asp Gln Val Asp		590
	595	600
Lys Glu Asp Glu Asp Phe Gln Glu Ser Asn Lys Met His Ser Met Asn		605
	610	615
Gly Phe Met Tyr Gly Asn Gln Pro Gly Leu Thr Met Cys Lys Gly Asp		620
625	630	635
Ser Val Val Trp Tyr Leu Phe Ser Ala Gly Asn Glu Ala Asp Val His		640
	645	650
Gly Ile Tyr Phe Ser Gly Asn Thr Tyr Leu Trp Arg Gly Glu Arg Arg		655
	660	665
Asp Thr Ala Asn Leu Phe Pro Gln Thr Ser Leu Thr Leu His Met Trp		670
	675	680
Pro Asp Thr Glu Gly Thr Phe Asn Val Glu Cys Leu Thr Thr Asp His		685
	690	695
Tyr Thr Gly Gly Met Lys Gln Lys Tyr Thr Val Asn Gln Cys Arg Arg		700
705	710	715
Gln Ser Glu Asp Ser Thr Phe Tyr Leu Gly Glu Arg Thr Tyr Tyr Ile		720
	725	730
Ala Ala Val Glu Val Glu Trp Asp Tyr Ser Pro Gln Arg Glu Trp Glu		735
	740	745
Lys Glu Leu His His Leu Gln Glu Gln Asn Val Ser Asn Ala Phe Leu		750

	755		760		765	
Asp	Lys Gly Glu Phe Tyr	Ile Gly Ser Lys Tyr	Lys Lys Val Val Tyr			
770		775	780			
Arg	Gln Tyr Thr Asp Ser	Thr Phe Arg Val Pro	Val Glu Arg Lys Ala			
785		790	795			800
Glu	Glu Glu His Leu Gly	Ile Leu Gly Pro Gln	Leu His Ala Asp Val			
	805	810	815			
Gly	Asp Lys Val Lys Ile	Ile Phe Lys Asn Met	Ala Thr Arg Pro Tyr			
	820	825	830			
Ser	Ile His Ala His Gly	Val Gln Thr Glu Ser	Ser Thr Val Thr Pro			
	835	840	845			
Thr	Leu Pro Gly Glu Thr	Leu Thr Tyr Val Trp	Lys Ile Pro Glu Arg			
	850	855	860			
Ser	Gly Ala Gly Thr Glu	Asp Ser Ala Cys Ile	Pro Trp Ala Tyr Tyr			
865		870	875			880
Ser	Thr Val Asp Gln Val	Lys Asp Leu Tyr Ser	Gly Leu Ile Gly Pro			
	885	890	895			
Leu	Ile Val Cys Arg Arg	Pro Tyr Leu Lys Val	Phe Asn Pro Arg Arg			
	900	905	910			
Lys	Leu Glu Phe Ala Leu	Leu Phe Val Phe Asp	Glu Asn Glu Ser			
	915	920	925			
Trp	Tyr Leu Asp Asp Asn	Ile Lys Thr Tyr Ser	Asp His Pro Glu Lys			
	930	935	940			
Val	Asn Lys Asp Asp Glu	Glu Phe Ile Glu Ser	Asn Lys Met His Ala			
945		950	955			960
Ile	Asn Gly Arg Met Phe	Gly Asn Leu Gln Gly	Leu Thr Met His Val			
	965	970	975			
Gly	Asp Glu Val Asn Trp	Tyr Leu Met Gly Met	Gly Asn Glu Ile Asp			
	980	985	990			
Leu	His Thr Val His Phe	His Gly His Ser Phe	Gln Tyr Lys His Arg			
	995	1000	1005			
Gly	Val Tyr Ser Ser Asp	Val Phe Asp Ile Phe	Pro Gly Thr Tyr Gln			
	1010	1015	1020			
Thr	Leu Glu Met Phe Pro	Arg Thr Pro Gly Ile	Trp Leu Leu His Cys			
1025		1030	1035			1040
His	Val Thr Asp His Ile	His Ala Gly Met Glu	Thr Thr Tyr Thr Val			
	1045	1050	1055			
Leu	Gln Asn Glu Ala Ser	Ser Glu Thr His Arg	Arg Ile Trp Asn Val			
	1060	1065	1070			
Ile	Tyr Pro Ile Thr Val	Ser Val Ile Ile Leu	Phe Gln Ile Ser Thr			
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<210> 62
 <211> 969
 <212> DNA
 <213> Homo sapiens

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75

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<210> 63

<211> 138

<212> PRT

<213> Homo sapiens

<400> 63

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20          25          30
Ala Val Ala Ala Ala Ser Lys Pro Ala Val Glu Ile Lys Gln Glu Gly
35          40          45
Asp Thr Phe Tyr Ile Lys Thr Ser Thr Thr Val Arg Thr Thr Glu Ile
50          55          60
Asn Phe Lys Val Gly Glu Glu Phe Glu Glu Gln Thr Val Asp Gly Arg
65          70          75          80
Pro Cys Lys Ser Leu Val Lys Trp Glu Ser Glu Asn Lys Met Val Cys
85          90          95
Glu Gln Lys Leu Leu Lys Gly Glu Gly Pro Lys Thr Ser Trp Thr Arg
100         105         110
Glu Leu Thr Asn Asp Gly Glu Leu Ile Leu Thr Met Thr Ala Asp Asp
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Val Val Cys Thr Arg Val Tyr Val Arg Glu
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<210> 64

<211> 927

<212> DNA

<213> Homo sapiens

<400> 64

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927

<210> 65

<211> 114

<212> PRT

<213> Homo sapiens

<400> 65

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			20					25					30		
Gly	Leu	Ile	Ala	Val	Ala	Val	Phe	Leu	Val	Leu	Val	Ala	Ile	Ala	Phe
			35				40					45			
Ala	Val	Asn	His	Phe	Trp	Cys	Gln	Glu	Glu	Pro	Glu	Pro	Ala	His	Met
			50				55				60				
Ile	Leu	Thr	Val	Gly	Asn	Lys	Ala	Asp	Gly	Val	Leu	Val	Gly	Thr	Asp
65					70					75				80	
Gly	Arg	Tyr	Ser	Ser	Met	Ala	Ala	Ser	Phe	Arg	Ser	Ser	Glu	His	Glu
				85					90					95	
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<210> 66

<211> 3641

<212> DNA

<213> Homo sapiens

<400> 66

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<210> 67

<211> 482

<212> PRT

<213> Homo sapiens

<400> 67

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Lys Arg Ser Met Lys Arg Asp Asp Thr Lys Asp Thr Tyr Lys Leu Pro
          35           40           45
His Arg Leu Ile Glu Lys Lys Arg Arg Asp Arg Ile Asn Glu Cys Ile
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Ala Gln Leu Lys Asp Leu Leu Pro Glu His Leu Lys Leu Thr Thr Leu
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Gly His Leu Glu Lys Ala Val Val Leu Glu Leu Thr Leu Lys His Leu
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Lys Ala Leu Thr Ala Leu Thr Glu Gln His Gln Lys Ile Ile Ala
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Leu Gln Asn Gly Glu Arg Ser Leu Lys Ser Pro Ile Gln Ser Asp Leu
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 Pro Ser Ala Ala Gly Ser Ala Ala Ala Pro Cys Leu Glu Arg Ala Gly
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 Gln Lys Leu Glu Pro Leu Ala Tyr Cys Val Pro Val Ile Gln Arg Thr
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 325 330 335
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 <212> DNA
 <213> Homo sapiens

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 <211> 341
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Gly Arg Leu Phe Ala Leu Glu Phe Ala Arg Arg Arg Ala Leu Leu Val
 50 55 60
 Leu Trp Asp Ile Asn Thr Gln Ser Asn Glu Glu Thr Ala Gly Met Val
 65 70 75 80
 Arg His Ile Tyr Arg Asp Leu Glu Ala Ala Asp Ala Ala Ala Leu Gln
 85 90 95
 Ala Gly Asn Gly Glu Glu Glu Ile Leu Pro His Cys Asn Leu Gln Val
 100 105 110
 Phe Thr Tyr Thr Cys Asp Val Gly Lys Arg Glu Asn Val Tyr Leu Thr
 115 120 125
 Ala Glu Arg Val Arg Lys Glu Val Gly Glu Val Ser Val Leu Val Asn
 130 135 140
 Asn Ala Gly Val Val Ser Gly His His Leu Leu Glu Cys Pro Asp Glu
 145 150 155 160
 Leu Ile Glu Arg Thr Met Met Val Asn Cys His Ala His Phe Trp Thr
 165 170 175
 Thr Lys Ala Phe Leu Pro Thr Met Leu Glu Ile Asn His Gly His Ile
 180 185 190
 Val Thr Val Ala Ser Ser Leu Gly Leu Phe Ser Thr Ala Gly Val Glu
 195 200 205
 Asp Tyr Cys Ala Ser Lys Phe Gly Val Val Gly Phe His Glu Ser Leu
 210 215 220
 Ser His Glu Leu Lys Ala Ala Glu Lys Asp Gly Ile Lys Thr Thr Leu
 225 230 235 240
 Val Cys Pro Tyr Leu Val Asp Thr Gly Met Phe Arg Gly Cys Arg Ile
 245 250 255
 Arg Lys Glu Ile Glu Pro Phe Leu Pro Pro Leu Lys Pro Asp Tyr Cys
 260 265 270
 Val Lys Gln Ala Met Lys Ala Ile Leu Thr Asp Gln Pro Met Ile Cys
 275 280 285
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 Ala Lys Asn Gly Ile
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<210> 70
 <211> 1428
 <212> DNA
 <213> Homo sapiens

<400> 70

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<210> 71

<211> 289

<212> PRT

<213> Homo sapiens

<400> 71

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 35          40          45
Ser Pro Thr Gly Gly Ala Pro His Gly Tyr Cys Ser Pro Thr Ser Ala
 50          55          60
Ser Tyr Gly Lys Ala Leu Asn Pro Tyr Gln Tyr Gln Tyr His Gly Val
 65          70          75          80
Asn Gly Ser Ala Gly Ser Tyr Pro Ala Lys Ala Tyr Ala Asp Tyr Ser
 85          90          95
Tyr Ala Ser Ser Tyr His Gln Tyr Gly Gly Ala Tyr Asn Arg Val Pro
100          105          110
Ser Ala Thr Asn Gln Pro Glu Lys Glu Val Thr Glu Pro Glu Val Arg
115          120          125
Met Val Asn Gly Lys Pro Lys Lys Val Arg Lys Pro Arg Thr Ile Tyr
130          135          140
Ser Ser Phe Gln Leu Ala Ala Leu Gln Arg Arg Phe Gln Lys Thr Gln
145          150          155          160
Tyr Leu Ala Leu Pro Glu Arg Ala Glu Leu Ala Ala Ser Leu Gly Leu
165          170          175
Thr Gln Thr Gln Val Lys Ile Trp Phe Gln Asn Lys Arg Ser Lys Ile
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Lys Lys Ile Met Lys Asn Gly Glu Met Pro Pro Glu His Ser Pro Ser
195          200          205
Ser Ser Asp Pro Met Ala Cys Asn Ser Pro Gln Ser Pro Ala Val Trp

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210	215	220
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Ala Ser Trp Tyr Thr Ser Ala Ala Ser Ser Ile Asn Ser His Leu Pro		255
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Tyr		

<210> 72
 <211> 2036
 <212> DNA
 <213> Homo sapiens

<400> 72

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<210> 73
 <211> 434
 <212> PRT
 <213> Homo sapiens

<400> 73

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 <211> 1907
 <212> DNA
 <213> Homo sapiens

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<210> 79

<211> 1051

<212> PRT

<213> Homo sapiens

<400> 79

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Met Lys Ser Glu Asp Tyr Pro His Glu Thr Met Ala Pro Asp Ile His
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Glu Glu Arg Gln Tyr Arg Cys Glu Asp Cys Asp Gln Leu Phe Glu Ser
20          25          30
Lys Ala Glu Leu Ala Asp His Gln Lys Phe Pro Cys Ser Thr Pro His
35          40          45
Ser Ala Phe Ser Met Val Glu Glu Asp Phe Gln Gln Lys Leu Glu Ser
50          55          60
Glu Asn Asp Leu Gln Glu Ile His Thr Ile Gln Glu Cys Lys Glu Cys
65          70          75          80
Asp Gln Val Phe Pro Asp Leu Gln Ser Leu Glu Lys His Met Leu Ser
85          90          95
His Thr Glu Glu Arg Glu Tyr Lys Cys Asp Gln Cys Pro Lys Ala Phe
100         105         110
Asn Trp Lys Ser Asn Leu Ile Arg His Gln Met Ser His Asp Ser Gly
115         120         125
Lys His Tyr Glu Cys Glu Asn Cys Ala Lys Val Phe Thr Asp Pro Ser
130         135         140
Asn Leu Gln Arg His Ile Arg Ser Gln His Val Gly Ala Arg Ala His
145         150         155         160
Ala Cys Pro Glu Cys Gly Lys Thr Phe Ala Thr Ser Ser Gly Leu Lys
165         170         175
Gln His Lys His Ile His Ser Ser Val Lys Pro Phe Ile Cys Glu Val
180         185         190
Cys His Lys Ser Tyr Thr Gln Phe Ser Asn Leu Cys Arg His Lys Arg
195         200         205
Met His Ala Asp Cys Arg Thr Gln Ile Lys Cys Lys Asp Cys Gly Gln
210         215         220
Met Phe Ser Thr Thr Ser Ser Leu Asn Lys His Arg Arg Phe Cys Glu
225         230         235         240
Gly Lys Asn His Phe Ala Ala Gly Gly Phe Phe Gly Gln Gly Ile Ser
245         250         255

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Leu	Pro	Gly	Thr	Pro	Ala	Met	Asp	Lys	Thr	Ser	Met	Val	Asn	Met	Ser	260	265	270
His	Ala	Asn	Pro	Gly	Leu	Ala	Asp	Tyr	Phe	Gly	Ala	Asn	Arg	His	Pro	275	280	285
Ala	Gly	Leu	Thr	Phe	Pro	Thr	Ala	Pro	Gly	Phe	Ser	Phe	Ser	Val	Pro	290	295	300
Gly	Leu	Phe	Pro	Ser	Gly	Leu	Tyr	His	Arg	Pro	Pro	Leu	Ile	Pro	Ala	305	310	315
Ser	Ser	Pro	Val	Lys	Gly	Leu	Ser	Ser	Thr	Glu	Gln	Thr	Asn	Lys	Ser	325	330	335
Gln	Ser	Pro	Leu	Met	Thr	His	Pro	Gln	Ile	Leu	Pro	Ala	Thr	Gln	Asp	340	345	350
Ile	Leu	Lys	Ala	Leu	Ser	Lys	His	Pro	Ser	Val	Gly	Asp	Asn	Lys	Pro	355	360	365
Val	Glu	Leu	Gln	Pro	Glu	Arg	Ser	Ser	Glu	Glu	Arg	Pro	Phe	Glu	Lys	370	375	380
Ile	Ser	Asp	Gln	Ser	Glu	Ser	Ser	Asp	Leu	Asp	Asp	Val	Ser	Thr	Pro	385	390	395
Ser	Gly	Ser	Asp	Leu	Glu	Thr	Thr	Ser	Gly	Ser	Asp	Leu	Glu	Ser	Asp	405	410	415
Ile	Glu	Ser	Asp	Lys	Glu	Lys	Phe	Lys	Glu	Asn	Gly	Lys	Met	Phe	Lys	420	425	430
Asp	Lys	Val	Ser	Pro	Leu	Gln	Asn	Leu	Ala	Ser	Ile	Asn	Asn	Lys	Lys	435	440	445
Glu	Tyr	Ser	Asn	His	Ser	Ile	Phe	Ser	Pro	Ser	Leu	Glu	Glu	Gln	Thr	450	455	460
Ala	Val	Ser	Gly	Ala	Val	Asn	Asp	Ser	Ile	Lys	Ala	Ile	Ala	Ser	Ile	465	470	475
Ala	Glu	Lys	Tyr	Phe	Gly	Ser	Thr	Gly	Leu	Val	Gly	Leu	Gln	Asp	Lys	485	490	495
Lys	Val	Gly	Ala	Leu	Pro	Tyr	Pro	Ser	Met	Phe	Pro	Leu	Pro	Phe	Phe	500	505	510
Pro	Ala	Phe	Ser	Gln	Ser	Met	Tyr	Pro	Phe	Pro	Asp	Arg	Asp	Leu	Arg	515	520	525
Ser	Leu	Pro	Leu	Lys	Met	Glu	Pro	Gln	Ser	Pro	Gly	Glu	Val	Lys	Lys	530	535	540
Leu	Gln	Lys	Gly	Ser	Ser	Glu	Ser	Pro	Phe	Asp	Leu	Thr	Thr	Lys	Arg	545	550	555
Lys	Asp	Glu	Lys	Pro	Leu	Thr	Pro	Val	Pro	Ser	Lys	Pro	Pro	Val	Thr	565	570	575
Pro	Ala	Thr	Ser	Gln	Asp	Gln	Pro	Leu	Asp	Leu	Ser	Met	Gly	Ser	Arg	580	585	590
Ser	Arg	Ala	Ser	Gly	Thr	Lys	Leu	Thr	Glu	Pro	Arg	Lys	Asn	His	Val	595	600	605
Phe	Gly	Gly	Lys	Lys	Gly	Ser	Asn	Val	Glu	Ser	Arg	Pro	Ala	Ser	Asp	610	615	620
Gly	Ser	Leu	Gln	His	Ala	Arg	Pro	Thr	Pro	Phe	Phe	Met	Asp	Pro	Ile	625	630	635
Tyr	Arg	Val	Glu	Lys	Arg	Lys	Leu	Thr	Asp	Pro	Leu	Glu	Ala	Leu	Lys	645	650	655
Glu	Lys	Tyr	Leu	Arg	Pro	Ser	Pro	Gly	Phe	Leu	Phe	His	Pro	Gln	Phe	660	665	670
Gln	Leu	Pro	Asp	Gln	Arg	Thr	Trp	Met	Ser	Ala	Ile	Glu	Asn	Met	Ala	675	680	685
Glu	Lys	Leu	Glu	Ser	Phe	Ser	Ala	Leu	Lys	Pro	Glu	Ala	Ser	Glu	Leu	690	695	700
Leu	Gln	Ser	Val	Pro	Ser	Met	Phe	Asn	Phe	Arg	Ala	Pro	Pro	Asn	Ala	705	710	715
																		720

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 Tyr Cys Gly Lys Ile Phe Pro Arg Ser Ala Asn Leu Thr Arg His Leu
 740 745 750
 Arg Thr His Thr Gly Glu Gln Pro Tyr Arg Cys Lys Tyr Cys Asp Arg
 755 760 765
 Ser Phe Ser Ile Ser Ser Asn Leu Gln Arg His Val Arg Asn Ile His
 770 775 780
 Asn Lys Glu Lys Pro Phe Lys Cys His Leu Cys Tyr Arg Cys Phe Gly
 785 790 795 800
 Gln Gln Thr Asn Leu Asp Arg His Leu Lys Lys His Glu Asn Gly Asn
 805 810 815
 Met Ser Gly Thr Ala Thr Ser Ser Pro His Ser Glu Leu Glu Ser Thr
 820 825 830
 Gly Ala Ile Leu Asp Asp Lys Glu Asp Ala Tyr Phe Thr Glu Ile Arg
 835 840 845
 Asn Phe Ile Gly Asn Ser Asn His Gly Ser Gln Ser Pro Arg Asn Val
 850 855 860
 Glu Glu Arg Met Asn Gly Ser His Phe Lys Glu Glu Lys Ala Leu Val
 865 870 875 880
 Pro Ser Gln Asn Ser Asp Leu Leu Asp Asp Glu Glu Val Glu Asp Glu
 885 890 895
 Val Leu Leu Asp Glu Glu Asp Glu Asp Tyr Asp Ile Thr Gly Lys Thr
 900 905 910
 Gly Lys Glu Pro Val Thr Ser Asn Leu His Glu Gly Asn Pro Glu Asp
 915 920 925
 Asp Tyr Glu Glu Thr Ser Ala Leu Glu Met Ser Cys Lys Thr Ser Pro
 930 935 940
 Val Arg Tyr Lys Glu Glu Glu Tyr Lys Ser Gly Leu Ser Ala Leu Asp
 945 950 955 960
 His Ile Arg His Phe Thr Asp Ser Leu Lys Met Arg Lys Met Glu Asp
 965 970 975
 Asn Gln Tyr Ser Glu Ala Glu Leu Ser Ser Phe Ser Thr Ser His Val
 980 985 990
 Pro Glu Glu Leu Lys Gln Pro Leu His Arg Lys Ser Lys Ser Gln Ala
 995 1000 1005
 Tyr Ala Met Met Leu Ser Leu Ser Asp Lys Glu Ser Leu His Ser Thr
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<210> 80
 <211> 3978
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(3978)
 <223> n = A,T,C or G

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 agctgggtca agtacattag attcgtggc tggtatgatc agcacaacct tgttgcattgc 180

cagataaatg	atcagatat	ctatagagta	gttgcgagaca	ttgcgccggg	agaggagctt	240
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atatttttatg	ctggtttgtct	gcaagcttgt	gcgatgttat	gttcatgtta	atcctattttg	3600
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cagttatattt gccctttatt gaggaaccag atttgttttc tttttgtttg taatctcatt 3720
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atgcctttca gtgcattact atgggaggag caactaaaaa ataaagactt acaaaaagga 3840
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<210> 81

<211> 727

<212> PRT

<213> Homo sapiens

<400> 81

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Met Lys Ser Glu Asp Tyr Pro His Glu Thr Met Ala Pro Asp Ile His
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 20          25          30
Lys Ala Glu Leu Ala Asp His Gln Lys Phe Pro Cys Ser Thr Pro His
 35          40          45
Ser Ala Phe Ser Met Val Glu Glu Asp Phe Gln Gln Lys Leu Glu Ser
 50          55          60
Glu Asn Asp Leu Gln Glu Ile His Thr Ile Gln Glu Cys Lys Glu Cys
 65          70          75          80
Asp Gln Val Phe Leu Asp Leu Gln Ser Leu Glu Lys His Met Leu Ser
 85          90          95
His Thr Glu Glu Arg Glu Tyr Lys Cys Asp Gln Cys Pro Lys Ala Phe
100          105          110
Asn Trp Lys Ser Asn Leu Ile Arg His Gln Met Ser His Asp Ser Gly
115          120          125
Lys His Tyr Glu Cys Glu Asn Cys Ala Lys Val Phe Thr Asp Pro Ser
130          135          140
Asn Leu Gln Arg His Ile Arg Ser Gln His Val Gly Ala Arg Ala His
145          150          155          160
Ala Cys Pro Glu Cys Gly Lys Thr Phe Ala Thr Ser Ser Gly Leu Lys
165          170          175
Gln His Lys His Ile His Ser Ser Val Lys Pro Phe Ile Ser Phe Ser
180          185          190
Gln Ser Met Tyr Pro Phe Pro Asp Arg Asp Leu Arg Ser Leu Pro Leu
195          200          205
Lys Met Glu Pro Gln Ser Pro Gly Glu Val Lys Lys Leu Gln Lys Gly
210          215          220
Ser Ser Glu Ser Pro Phe Asp Leu Thr Thr Lys Arg Lys Asp Glu Lys
225          230          235          240
Pro Leu Thr Pro Val Pro Ser Lys Pro Pro Val Thr Pro Ala Thr Ser
245          250          255
Gln Asp Gln Pro Leu Asp Leu Ser Met Gly Ser Arg Ser Arg Ala Ser
260          265          270
Gly Thr Lys Leu Thr Glu Pro Arg Lys Asn His Val Phe Gly Gly Lys
275          280          285
Lys Gly Ser Asn Val Glu Ser Arg Pro Ala Ser Asp Gly Ser Leu Gln
290          295          300
His Ala Arg Pro Thr Pro Phe Phe Met Asp Pro Ile Tyr Arg Val Glu
305          310          315          320
Lys Arg Lys Leu Thr Asp Pro Leu Glu Ala Leu Lys Glu Lys Tyr Leu
325          330          335
Arg Pro Ser Pro Gly Phe Leu Phe His Pro Gln Phe Gln Leu Pro Asp
340          345          350
Gln Arg Thr Trp Met Ser Ala Ile Glu Asn Met Ala Glu Lys Leu Glu

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Ser	Phe	Ser	Ala	Leu	Lys	Pro	Glu	Ala	Ser	Glu	Leu	Leu	Gln	Ser	Val
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Pro	Ser	Met	Phe	Asn	Phe	Arg	Ala	Pro	Pro	Asn	Ala	Leu	Pro	Glu	Asn
385				390						395					400
Leu	Leu	Arg	Lys	Gly	Lys	Glu	Arg	Tyr	Thr	Cys	Arg	Tyr	Cys	Gly	Lys
				405					410					415	
Ile	Phe	Pro	Arg	Ser	Ala	Asn	Leu	Thr	Arg	His	Leu	Arg	Thr	His	Thr
				420				425					430		
Gly	Glu	Gln	Pro	Tyr	Arg	Cys	Lys	Tyr	Cys	Asp	Arg	Ser	Phe	Ser	Ile
		435					440					445			
Ser	Ser	Asn	Leu	Gln	Arg	His	Val	Arg	Asn	Ile	His	Asn	Lys	Glu	Lys
	450					455					460				
Pro	Phe	Lys	Cys	His	Leu	Cys	Tyr	Arg	Cys	Phe	Gly	Gln	Gln	Thr	Asn
465				470						475					480
Leu	Asp	Arg	His	Leu	Lys	Lys	His	Glu	Asn	Gly	Asn	Met	Ser	Gly	Thr
				485					490					495	
Ala	Thr	Ser	Ser	Pro	His	Ser	Glu	Leu	Glu	Ser	Thr	Gly	Ala	Ile	Leu
			500					505					510		
Asp	Asp	Lys	Glu	Asp	Ala	Tyr	Phe	Thr	Glu	Ile	Arg	Asn	Phe	Ile	Gly
		515					520					525			
Asn	Ser	Asn	His	Gly	Ser	Gln	Ser	Pro	Arg	Asn	Val	Glu	Glu	Arg	Met
	530					535					540				
Asn	Gly	Ser	His	Phe	Lys	Glu	Glu	Lys	Ala	Leu	Val	Pro	Ser	Gln	Asn
545				550						555					560
Ser	Asp	Leu	Leu	Asp	Glu	Glu	Val	Glu	Asp	Glu	Val	Leu	Leu	Asp	
				565				570					575		
Glu	Glu	Asp	Glu	Asp	Tyr	Asp	Ile	Thr	Gly	Lys	Thr	Gly	Lys	Glu	Pro
			580					585					590		
Val	Thr	Ser	Asn	Leu	His	Glu	Gly	Asn	Pro	Glu	Asp	Asp	Tyr	Glu	Glu
		595					600					605			
Thr	Ser	Ala	Leu	Glu	Met	Ser	Cys	Lys	Thr	Ser	Pro	Val	Arg	Tyr	Lys
	610					615					620				
Glu	Glu	Glu	Tyr	Lys	Ser	Gly	Leu	Ser	Ala	Leu	Asp	His	Ile	Arg	His
625				630						635					640
Phe	Thr	Asp	Ser	Leu	Lys	Met	Arg	Lys	Met	Glu	Asp	Asn	Gln	Tyr	Ser
				645					650					655	
Glu	Ala	Glu	Leu	Ser	Ser	Phe	Ser	Thr	Ser	His	Val	Pro	Glu	Glu	Leu
			660					665					670		
Lys	Gln	Pro	Leu	His	Arg	Lys	Ser	Lys	Ser	Gln	Ala	Tyr	Ala	Met	Met
		675					680					685			
Leu	Ser	Leu	Ser	Asp	Lys	Glu	Ser	Leu	His	Ser	Thr	Ser	His	Ser	Ser
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<210> 82
<211> 4923
<212> DNA
<213> Homo sapiens
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<222> (1)...(4923)
<223> n = A,T,C or G
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cagataaatg	atcagatat	ctatagagta	gttgcagaca	ttgcgcgggg	agaggagctt	240
ctgctgttca	tgaagagcga	agactatccc	catgaaacta	tggcgccgga	tatccacgaa	300
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<212> DNA
<213> Homo sapiens
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<210> 85

<211> 595

<212> PRT

<213> Homo sapiens

<400> 85

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Val Gly Ser Gly Ile Ser Phe Gln Pro Gly Ala Ile Gly Val Glu Val
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Ser Ala Met Asn Pro Val Asn Ala Thr Ala Leu Tyr Ile Ser Ala Ser
20      25      30
Arg Leu Val Leu Asn Tyr Asp Pro Gly Asp Pro Lys Ala Phe Thr Glu
35      40      45
Ile Asn Arg Leu Leu Pro Tyr Phe Arg Gln Ser Leu Ser Cys Cys Val
50      55      60
Cys Gly His Leu Leu Gln Asp Pro Ile Ala Pro Thr Asn Ser Thr Cys
65      70      75      80
Gln His Tyr Val Cys Lys Thr Cys Lys Gly Lys Lys Met Met Met Lys
85      90      95
Pro Ser Cys Ser Trp Cys Lys Asp Tyr Glu Gln Phe Glu Glu Asn Lys
100     105     110
Gln Leu Ser Ile Leu Val Asn Cys Tyr Lys Lys Leu Cys Glu Tyr Ile
115     120     125
Thr Gln Thr Thr Leu Ala Arg Asp Ile Ile Glu Ala Val Asp Cys Ser
130     135     140
Ser Asp Ile Leu Ala Leu Leu Asn Asp Gly Ser Leu Phe Cys Glu Glu
145     150     155     160
Thr Glu Lys Pro Ser Asp Ser Ser Phe Thr Leu Cys Leu Thr His Ser
165     170     175
Pro Leu Pro Ser Thr Ser Glu Pro Thr Thr Asp Pro Gln Ala Ser Leu
180     185     190
Ser Pro Met Ser Glu Ser Thr Leu Ser Ile Ala Ile Gly Ser Ser Val
195     200     205
Ile Asn Gly Leu Pro Thr Tyr Asn Gly Leu Ser Ile Asp Arg Phe Gly
210     215     220
Ile Asn Ile Pro Ser Pro Glu His Ser Asn Thr Ile Asp Val Cys Asn
225     230     235     240
Thr Val Asp Ile Lys Thr Glu Asp Leu Ser Asp Ser Leu Pro Pro Val
245     250     255
Cys Asp Thr Val Ala Thr Asp Leu Cys Ser Thr Gly Ile Asp Ile Cys
260     265     270
Ser Phe Ser Glu Asp Ile Lys Pro Gly Asp Ser Leu Leu Leu Ser Val
275     280     285
Glu Glu Val Leu Arg Ser Leu Glu Thr Val Ser Asn Thr Glu Val Cys
290     295     300
Cys Pro Asn Leu Gln Pro Asn Leu Glu Ala Thr Val Ser Asn Gly Pro
305     310     315     320
Phe Leu Gln Leu Ser Ser Gln Ser Leu Ser His Asn Val Phe Met Ser

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				325					330					335			
Thr	Ser	Pro	Ala	Leu	His	Gly	Leu	Ser	Cys	Thr	Ala	Ala	Thr	Pro	Lys		
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Ile	Ala	Lys	Leu	Asn	Arg	Lys	Arg	Ser	Arg	Ser	Glu	Ser	Asp	Ser	Glu		
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Lys	Val	Gln	Pro	Leu	Pro	Ile	Ser	Thr	Ile	Ile	Arg	Gly	Pro	Thr	Leu		
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Gly	Ala	Ser	Ala	Pro	Val	Thr	Val	Lys	Arg	Glu	Ser	Lys	Ile	Ser	Leu		
385					390					395					400		
Gln	Pro	Ile	Ala	Thr	Val	Pro	Asn	Gly	Gly	Thr	Thr	Pro	Lys	Ile	Ser		
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Lys	Thr	Val	Leu	Leu	Ser	Thr	Lys	Ser	Met	Lys	Lys	Ser	His	Glu	His		
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		435					440					445					
Asp	Lys	Ala	Val	Lys	Glu	Lys	Ile	Pro	Ser	His	His	Phe	Met	Pro	Gly		
450						455					460						
Ser	Pro	Thr	Lys	Thr	Val	Tyr	Lys	Lys	Pro	Gln	Glu	Lys	Lys	Gly	Cys		
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Lys	Cys	Gly	Arg	Ala	Thr	Gln	Asn	Pro	Ser	Val	Leu	Thr	Cys	Arg	Gly		
				485				490						495			
Gln	Arg	Cys	Pro	Cys	Tyr	Ser	Asn	Arg	Lys	Ala	Cys	Leu	Asp	Cys	Ile		
			500					505					510				
Cys	Arg	Gly	Cys	Gln	Asn	Ser	Tyr	Met	Ala	Asn	Gly	Glu	Lys	Lys	Leu		
		515					520					525					
Glu	Ala	Phe	Ala	Val	Pro	Glu	Lys	Ala	Leu	Glu	Gln	Thr	Arg	Leu	Thr		
		530				535					540						
Leu	Gly	Ile	Asn	Val	Thr	Ser	Ile	Ala	Val	Arg	Asn	Ala	Ser	Thr	Ser		
545					550					555					560		
Thr	Ser	Val	Ile	Asn	Val	Thr	Gly	Ser	Pro	Val	Thr	Thr	Phe	Leu	Ala		
				565				570						575			
Ala	Ser	Thr	His	Asp	Asp	Lys	Ser	Leu	Asp	Glu	Ala	Ile	Asp	Met	Arg		
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Phe	Asp	Cys															
		595															

<210> 86
 <211> 1385
 <212> DNA
 <213> Homo sapiens

<400> 86
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 aagactttta tgttcataca gtaatgactt gttatttttag tttattttgga atagacaata 240
 tggctcctag tcctgggtcat atattgagag tttacgggtg tgttttgcct tgggtctgttg 300
 ctttgactg gctcacagaa aagccagaac tgtttcaact agcactgaaa gcattcaggt 360
 atactctgaa actaatgatt gataaagcaa gtttaggtcc aatagaagac tttagagaac 420
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 agttaaatcc tgaagctggt agaggtcagt gggccaatct ttcatgggaa ttactttatg 660
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<210> 87
 <211> 252
 <212> PRT
 <213> Homo sapiens

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<400> 87
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20     25     30
Lys Ala Ser Asn Val Leu Glu Glu Ile Ala Lys Asp Lys Val Leu Lys
35     40     45
Asp Phe Tyr Val His Thr Val Met Thr Cys Tyr Phe Ser Leu Phe Gly
50     55     60
Ile Asp Asn Met Ala Pro Ser Pro Gly His Ile Leu Arg Val Tyr Gly
65     70     75     80
Gly Val Leu Pro Trp Ser Val Ala Leu Asp Trp Leu Thr Glu Lys Pro
85     90     95
Glu Leu Phe Gln Leu Ala Leu Lys Ala Phe Arg Tyr Thr Leu Lys Leu
100    105    110
Met Ile Asp Lys Ala Ser Leu Gly Pro Ile Glu Asp Phe Arg Glu Leu
115    120    125
Ile Lys Tyr Leu Glu Glu Tyr Glu Arg Asp Trp Tyr Ile Gly Leu Val
130    135    140
Ser Asp Glu Lys Trp Lys Glu Ala Ile Leu Gln Glu Lys Pro Tyr Leu
145    150    155    160
Phe Ser Leu Gly Tyr Asp Ser Asn Met Gly Ile Tyr Thr Gly Arg Val
165    170    175
Leu Ser Leu Gln Glu Leu Leu Ile Gln Val Gly Lys Leu Asn Pro Glu
180    185    190
Ala Val Arg Gly Gln Trp Ala Asn Leu Ser Trp Glu Leu Leu Tyr Ala
195    200    205
Thr Asn Asp Asp Glu Glu Arg Tyr Ser Ile Gln Ala His Pro Leu Leu
210    215    220
Leu Arg Asn Leu Thr Val Gln Ala Ala Glu Pro Pro Leu Gly Tyr Pro
225    230    235    240
Ile Tyr Ser Ser Lys Pro Leu His Ile His Leu Tyr
245    250

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<210> 88
 <211> 4660
 <212> DNA
 <213> Homo sapiens

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<400> 88
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<210> 89

<211> 538

<212> PRT

<213> Homo sapiens

<400> 89

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Met Phe Thr Tyr Lys Arg Pro Asn Glu Ile Ser Ser Thr Ala Gly Glu
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          20          25          30
Ile His Gln Gln Pro Asn Pro Gly Val His Tyr Glu Tyr Val Ile Met
          35          40          45
Gly Thr Asn Ala Ile Ser Pro Gln Val Pro Pro His Arg Arg Pro Gly
          50          55          60
Glu Pro Phe Asn Gly Gln Met Val Thr Glu Gly Arg Ser Gln Glu Glu
65          70          75          80
Gly Glu Gln Lys Gly Arg Asn Glu Glu Lys Glu Asp Leu Arg Gly Glu
          85          90          95
Ala Pro Glu Met Phe Thr Ser Glu Ser Ala Gln Thr Phe Pro Val Arg
          100          105          110
His Pro Asp Arg Phe Ser Pro His Arg Pro Asp Asn Leu Val Pro Pro
          115          120          125
Ala Pro Gln Pro Pro Arg Arg Ser Arg Asp His Asn Trp Lys Gln Leu
          130          135          140
Gly Thr Thr Glu Cys Ser Thr Thr Cys Gly Lys Gly Ser Gln Tyr Pro
145          150          155          160
Ile Phe Arg Cys Val His Arg Ser Thr His Glu Glu Ala Pro Glu Ser
          165          170          175
Tyr Cys Asp Ser Ser Met Lys Pro Thr Pro Glu Glu Glu Pro Cys Asn
          180          185          190
Ile Phe Pro Cys Pro Ala Phe Trp Asp Ile Gly Glu Trp Ser Glu Cys
          195          200          205
Ser Lys Thr Cys Gly Leu Gly Met Gln His Arg Gln Val Leu Cys Arg
          210          215          220
Gln Val Tyr Ala Asn Arg Ser Leu Thr Val Gln Pro Tyr Arg Cys Gln
225          230          235          240
His Leu Glu Lys Pro Glu Thr Thr Ser Thr Cys Gln Leu Lys Ile Cys
          245          250          255
Ser Glu Trp Gln Ile Arg Thr Asp Trp Thr Ser Cys Ser Val Pro Cys

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<210> 91

<211> 625

<212> PRT

<213> Homo sapiens

<400> 91

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Asp Glu Ala Trp Lys Ser Tyr Leu Glu Asn Pro Leu Thr Ala Ala Thr
35      40      45
Lys Ala Met Met Ile Ile Asn Gly Asp Glu Asp Ser Ala Ala Ala Leu
50      55      60
Gly Leu Leu Tyr Asp Tyr Tyr Lys Val Pro Arg Asp Lys Arg Leu Leu
65      70      75      80
Ser Val Ser Lys Ala Ser Asp Ser Gln Glu Asp Gln Glu Lys Arg Asn
85      90      95
Cys Leu Gly Thr Ser Glu Ala Gln Ser Asn Leu Ser Gly Gly Glu Asn
100     105     110
Arg Val Gln Val Leu Lys Thr Val Pro Val Asn Leu Ser Leu Asn Gln
115     120     125
Asp His Leu Glu Asn Ser Lys Arg Glu Gln Tyr Ser Ile Ser Phe Pro
130     135     140
Glu Ser Ser Ala Ile Ile Pro Val Ser Gly Ile Thr Val Val Lys Ala
145     150     155     160
Glu Asp Phe Thr Pro Val Phe Met Ala Pro Pro Val His Tyr Pro Arg
165     170     175
Gly Asp Gly Glu Gln Arg Val Val Ile Phe Glu Gln Thr Gln Tyr
180     185     190
Asp Val Pro Ser Leu Ala Thr His Ser Ala Tyr Leu Lys Asp Asp Gln
195     200     205
Arg Ser Thr Pro Asp Ser Thr Tyr Ser Glu Ser Phe Lys Asp Ala Ala
210     215     220
Thr Glu Lys Phe Arg Ser Ala Ser Val Gly Ala Glu Glu Tyr Met Tyr
225     230     235     240
Asp Gln Thr Ser Ser Gly Thr Phe Gln Tyr Thr Leu Glu Ala Thr Lys
245     250     255
Ser Leu Arg Gln Lys Gln Gly Glu Gly Pro Met Thr Tyr Leu Asn Lys
260     265     270
Gly Gln Phe Tyr Ala Ile Thr Leu Ser Glu Thr Gly Asp Asn Lys Cys
275     280     285
Phe Arg His Pro Ile Ser Lys Val Arg Ser Val Val Met Val Val Phe
290     295     300
Ser Glu Asp Lys Asn Arg Asp Glu Gln Leu Lys Tyr Trp Lys Tyr Trp
305     310     315     320
His Ser Arg Gln His Thr Ala Lys Gln Arg Val Leu Asp Ile Ala Asp
325     330     335
Tyr Lys Glu Ser Phe Asn Thr Ile Gly Asn Ile Glu Glu Ile Ala Tyr
340     345     350

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Asn Ala Val Ser Phe Thr Trp Asp Val Asn Glu Glu Ala Lys Ile Phe
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 370 375 380
 Lys Gly Leu Pro Leu Met Ile Gln Ile Asp Thr Tyr Ser Tyr Asn Asn
 385 390 395 400
 Arg Ser Asn Lys Pro Ile His Arg Ala Tyr Cys Gln Ile Lys Val Phe
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 Cys Asp Lys Gly Ala Glu Arg Lys Ile Arg Asp Glu Glu Gln Lys Gln
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 Asn Arg Lys Asn Gly Lys Gly Gln Ala Ser Gln Thr Gln Cys Asn Ser
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 Ser Ser Asp Gly Lys Leu Ala Ala Ile Pro Leu Gln Lys Lys Ser Asp
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 Ile Thr Tyr Phe Lys Thr Met Pro Asp Leu His Ser Gln Pro Val Leu
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 Tyr Tyr Asn Thr Asp Asp Glu Arg Glu Gly Gly Ser Val Leu Val Lys
 500 505 510
 Arg Met Phe Arg Pro Met Glu Glu Glu Phe Gly Pro Val Pro Ser Lys
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 Gln Met Lys Glu Glu Gly Thr Lys Arg Val Leu Leu Tyr Val Arg Lys
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 Glu Thr Asp Asp Val Phe Asp Ala Leu Met Leu Lys Ser Pro Thr Val
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 Met Gly Leu Met Glu Ala Ile Ser Glu Lys Tyr Gly Leu Pro Val Glu
 565 570 575
 Lys Ile Ala Lys Leu Tyr Lys Lys Ser Lys Lys Gly Ile Leu Val Asn
 580 585 590
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<210> 92
 <211> 2085
 <212> DNA
 <213> Homo sapiens

<400> 92
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<210> 93

<211> 301

<212> PRT

<213> Homo sapiens

<400> 93

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 20          25          30
Gly Glu Glu Glu Arg Ala His Gln Ser Ile Leu Thr Gln Arg Val His
 35          40          45
Trp Ala Glu Ala Leu Gln Lys Leu Asp Thr Ile Arg Thr Gly Leu Val
 50          55          60
Gly Met Leu Thr His Leu Asp Asp Leu Gln Leu Ile Gln Lys Glu Gln
 65          70          75          80
Glu Ile Phe Glu Arg Thr Glu Glu Ala Glu Gly Ile Leu Asp Pro Gln
 85          90          95
Glu Ser Glu Met Leu Asn Phe Asn Glu Lys Cys Thr Arg Ser Pro Leu
 100         105         110
Leu Thr Gln Leu Trp Ala Thr Ala Val Leu Gly Ser Leu Ser Gly Thr
 115         120         125
Glu Asp Ile Arg Ile Asp Glu Arg Thr Val Ser Pro Phe Leu Gln Leu
 130         135         140
Ser Asp Asp Arg Lys Thr Leu Thr Phe Ser Thr Lys Lys Ser Lys Ala
 145         150         155         160
Cys Ala Asp Gly Pro Glu Arg Phe Asp His Trp Pro Asn Ala Leu Ala
 165         170         175
Ala Thr Ser Phe Gln Asn Gly Leu His Ala Trp Met Val Asn Val Gln
 180         185         190
Asn Ser Cys Ala Tyr Lys Val Gly Val Ala Ser Gly His Leu Pro Arg
 195         200         205
Lys Gly Ser Gly Ser Asp Cys Arg Leu Gly His Asn Ala Phe Ser Trp
 210         215         220
Val Phe Ser Arg Tyr Asp Gln Glu Phe Arg Phe Ser His Asn Gly Gln
 225         230         235         240

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His	Glu	Pro	Leu	Gly	Leu	Leu	Arg	Gly	Pro	Ala	Gln	Leu	Gly	Val	Val
				245					250					255	
Leu	Asp	Leu	Gln	Val	Gln	Glu	Leu	Leu	Phe	Tyr	Glu	Pro	Ala	Ser	Gly
			260					265					270		
Ile	Val	Leu	Cys	Ala	His	His	Val	Ser	Phe	Pro	Gly	Pro	Leu	Phe	Pro
		275					280					285			
Val	Phe	Ala	Val	Ala	Asp	Gln	Thr	Ile	Ser	Ile	Val	Arg			
	290					295					300				

<210> 94
 <211> 2317
 <212> DNA
 <213> Homo sapiens

<400> 94
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<210> 95
 <211> 626

<212> PRT

<213> Homo sapiens

<400> 95

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 20          25          30
Leu Thr Cys Leu Cys Pro Gln Cys Leu Ser Val Glu Asp Ala Leu Gly
 35          40          45
Leu Gly Glu Pro Glu Gly Ser Gly Leu Pro Pro Gly Pro Val Leu Glu
 50          55          60
Ala Arg Tyr Val Ala Arg Leu Ser Ala Ala Ala Val Leu Tyr Leu Ser
 65          70          75          80
Asn Pro Glu Gly Thr Cys Glu Asp Ala Arg Ala Gly Leu Trp Ala Ser
 85          90          95
His Ala Asp His Leu Leu Ala Leu Leu Glu Ser Pro Lys Ala Leu Thr
 100          105          110
Pro Gly Leu Ser Trp Leu Leu Gln Arg Met Gln Ala Arg Ala Ala Gly
 115          120          125
Gln Thr Pro Lys Thr Ala Cys Val Asp Ile Pro Gln Leu Leu Glu Glu
 130          135          140
Ala Val Gly Ala Gly Ala Pro Gly Ser Ala Gly Gly Val Leu Ala Ala
 145          150          155          160
Leu Leu Asp His Val Arg Ser Gly Ser Cys Phe His Ala Leu Pro Ser
 165          170          175
Pro Gln Tyr Phe Val Asp Phe Val Phe Gln Gln His Ser Ser Glu Val
 180          185          190
Pro Met Thr Leu Ala Glu Leu Ser Ala Leu Met Gln Arg Leu Gly Val
 195          200          205
Gly Arg Glu Ala His Ser Asp His Ser His Arg His Arg Gly Ala Ser
 210          215          220
Ser Arg Asp Pro Val Pro Leu Ile Ser Ser Ser Asn Ser Ser Ser Val
 225          230          235          240
Trp Asp Thr Val Cys Leu Ser Ala Arg Asp Val Met Ala Ala Tyr Gly
 245          250          255
Leu Ser Glu Gln Ala Gly Val Thr Pro Glu Ala Trp Ala Gln Leu Ser
 260          265          270
Pro Ala Leu Leu Gln Gln Gln Leu Ser Gly Ala Tyr Thr Ser Gln Ser
 275          280          285
Arg Pro Pro Val Gln Asp Gln Leu Ser Gln Ser Glu Arg Tyr Leu Tyr
 290          295          300
Gly Ser Leu Ala Thr Leu Leu Ile Cys Leu Cys Ala Val Phe Gly Leu
 305          310          315          320
Leu Leu Leu Thr Cys Thr Gly Cys Arg Gly Val Ala His Tyr Ile Leu
 325          330          335
Gln Thr Phe Leu Ser Leu Ala Val Gly Ala Leu Thr Gly Asp Ala Val
 340          345          350
Leu His Leu Thr Pro Lys Val Leu Gly Leu His Thr His Ser Glu Glu
 355          360          365
Gly Leu Ser Pro Gln Pro Thr Trp Arg Leu Leu Ala Met Leu Ala Gly
 370          375          380
Leu Tyr Ala Phe Phe Leu Phe Glu Asn Leu Phe Asn Leu Leu Leu Pro
 385          390          395          400
Arg Asp Pro Glu Asp Leu Glu Asp Gly Pro Cys Gly His Ser Ser His
 405          410          415
Ser His Gly Gly His Ser His Gly Val Ser Leu Gln Leu Ala Pro Ser
 420          425          430

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Glu Leu Arg Gln Pro Lys Pro Pro His Glu Gly Ser Arg Ala Asp Leu
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 Val Ala Glu Glu Ser Pro Glu Leu Leu Asn Pro Glu Pro Arg Arg Leu
 450 455 460
 Ser Pro Glu Leu Arg Leu Leu Pro Tyr Met Ile Thr Leu Gly Asp Ala
 465 470 475 480
 Val His Asn Phe Ala Asp Gly Leu Ala Val Gly Ala Ala Phe Ala Ser
 485 490 495
 Ser Trp Lys Thr Gly Leu Ala Thr Ser Leu Ala Val Phe Cys His Glu
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<210> 96

<211> 2761

<212> DNA

<213> Homo sapiens

<400> 96

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<212> PRT
<213> Homo sapiens

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 210         215         220

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<211> 2757

<212> DNA

<213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

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 Val Val Ile Pro Lys Lys Lys Thr Trp Asp Lys Val Ala Val Leu Gln
 65 70 75 80
 Ala Leu Ala Ser Thr Val Asn Arg Asp Thr Thr Ala Val Pro Tyr Val
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 Phe Gln Asp Asp Pro Tyr Leu Met Pro Ala Ser Ser Leu Glu Ser Arg
 100 105 110
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 115 120 125
 Ile Asn Ser Tyr Pro Lys Tyr Phe Gln Lys Asp Ile Ala Glu Pro His
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 145 150 155 160
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 Ser Val Asp Met Phe Asp Gln Leu Leu Gln Ala Gly Thr Thr Val Ser
 180 185 190
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 195 200 205
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 210 215 220
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 <213> Homo sapiens

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 <211> 280
 <212> PRT
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119

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<210> 103
 <211> 414
 <212> PRT
 <213> Homo sapiens

<400> 103

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			20					25					30		
Ala	Glu	Ser	Leu	Ser	Pro	Ile	Gly	Asp	Met	Lys	Val	Lys	Gly	Glu	Ala
			35				40					45			
Pro	Ala	Asn	Ser	Gly	Ala	Pro	Ala	Gly	Ala	Ala	Gly	Arg	Ala	Lys	Gly
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Asp	Glu	Arg	Lys	Arg	Leu	Ala	Gln	Gln	Asn	Pro	Asp	Leu	His	Asn	Ala
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			115				120					125			
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			130			135					140				
Val	Lys	Arg	Leu	Lys	Arg	Val	Glu	Gly	Gly	Phe	Leu	His	Gly	Leu	Ala
145					150					155					160
Glu	Pro	Gln	Ala	Ala	Ala	Leu	Gly	Pro	Glu	Gly	Gly	Arg	Val	Ala	Met
				165					170					175	
Asp	Gly	Leu	Gly	Leu	Gln	Phe	Pro	Glu	Gln	Gly	Phe	Pro	Ala	Gly	Pro
			180					185					190		
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			195				200					205			
Leu	Gly	Ala	Pro	Pro	Leu	Asp	Gly	Tyr	Pro	Leu	Pro	Thr	Pro	Asp	Thr
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			260					265						270	
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			275				280					285			
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			290			295					300				
Ala	Gly	Gly	Gly	Arg	Gly	Phe	Gln	Met	Gln	Pro	Gln	His	Gln	His	Gln
305					310					315					320
His	Gln	His	Gln	His	His	Pro	Pro	Gly	Pro	Gly	Gln	Pro	Ser	Pro	Pro
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121

	340		345		350
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	355		360		365
Phe Val Cys Lys Pro Glu Met Gly Leu Pro Tyr Gln Gly His Asp Ser					
	370		375		380
Gly Val Asn Leu Pro Asp Ser His Gly Ala Ile Ser Ser Val Val Ser					
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Asp Ala Ser Ser Ala Val Tyr Tyr Cys Asn Tyr Pro Asp Val					
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<210> 104
 <211> 2398
 <212> DNA
 <213> Homo sapiens

<400> 104
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<210> 105
 <211> 232
 <212> PRT
 <213> Homo sapiens

<400> 105
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 35 40 45
 Phe Ala Ala Ala Met Gly Val Pro Glu Ile Pro Gly Glu Lys Leu Val
 50 55 60
 Thr Glu Arg Asn Lys Lys Arg Leu Glu Lys Glu Lys His Glu Lys Gly
 65 70 75 80
 Ala Gln Lys Thr Asp Cys Gln Lys Asn Leu Gly Thr Val Gly Ala Val
 85 90 95
 Ala Leu Asp Cys Lys Gly Asn Val Ala Tyr Ala Thr Ser Thr Gly Gly
 100 105 110
 Ile Val Asn Lys Met Val Gly Arg Val Gly Asp Ser Pro Cys Leu Gly
 115 120 125
 Ala Gly Gly Tyr Ala Asp Asn Asp Ile Gly Ala Val Ser Thr Thr Gly
 130 135 140
 His Gly Glu Ser Ile Leu Lys Val Asn Leu Ala Arg Leu Thr Leu Phe
 145 150 155 160
 His Ile Glu Gln Gly Lys Thr Val Glu Glu Ala Ala Asp Leu Ser Leu
 165 170 175
 Gly Tyr Met Lys Ser Arg Val Lys Gly Leu Gly Gly Leu Ile Val Val
 180 185 190
 Ser Lys Thr Gly Asp Trp Val Ala Lys Trp Thr Ser Thr Ser Met Pro
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 Trp Ala Ala Ala Lys Asp Gly Lys Leu His Phe Gly Ile Asp Pro Asp
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 Asp Thr Thr Ile Thr Asp Leu Pro
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<210> 106
 <211> 1811
 <212> DNA
 <213> Homo sapiens

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<210> 107

<211> 282

<212> PRT

<213> Homo sapiens

<400> 107

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Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser
20      25      30
Gly Arg His Ser Ile Thr Val Thr Thr Val Ala Ser Ala Gly Asn Ile
35      40      45
Gly Glu Asp Gly Ile Gln Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu
50      55      60
Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val
65      70      75      80
His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met
85      90      95
Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn
100     105     110
Ala Ser Leu Arg Leu Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr
115     120     125
Lys Cys Tyr Ile Ile Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu
130     135     140
Tyr Lys Thr Gly Ala Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn
145     150     155     160
Ala Ser Ser Glu Thr Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln
165     170     175
Pro Thr Val Val Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser
180     185     190
Glu Val Ser Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met
195     200     205
Lys Val Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser
210     215     220
Cys Met Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val
225     230     235     240
Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser
245     250     255
Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu
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Leu Pro Leu Ser Pro Tyr Leu Met Leu Lys
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<210> 108
 <211> 2611
 <212> DNA
 <213> Homo sapiens

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<210> 109
 <211> 150
 <212> PRT

125

<213> Homo sapiens

<400> 109

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 20           25           30
Asn Ala Asp Gly His Gly Glu Val Trp Thr Asp Trp Asn Asn Met Ser
 35           40           45
Lys Phe Phe Gln Tyr Gly Trp Arg Cys Thr Thr Asn Glu Asn Thr Tyr
 50           55           60
Ser Asn Arg Thr Leu Met Gly Asn Trp Asn Gln Glu Arg Tyr Asp Leu
 65           70           75           80
Arg Asn Ile Val Gln Pro Lys Pro Leu Pro Ser Gln Phe Gly His Tyr
 85           90           95
Phe Glu Thr Thr Tyr Asp Thr Ser Tyr Asn Asn Lys Met Pro Leu Ser
 100          105          110
Thr His Arg Phe Lys Arg Glu Pro His Trp Phe Pro Gly His Gln Pro
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<210> 110

<211> 1032

<212> DNA

<213> Homo sapiens

<400> 110

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1032

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<210> 111

<211> 257

<212> PRT

<213> Homo sapiens

<400> 111

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126

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 35 40 45
 Pro Glu Asp Lys Leu His Glu Gln Cys Arg Pro Trp Arg Lys Asn Ala
 50 55 60
 Cys Cys Ser Thr Asn Thr Ser Gln Glu Ala His Lys Asp Val Ser Tyr
 65 70 75 80
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 Lys Arg His Phe Ile Gln Asp Thr Cys Leu Tyr Glu Cys Ser Pro Asn
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 Leu Gly Pro Trp Ile Gln Gln Val Asp Gln Ser Trp Arg Lys Glu Arg
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 Val Leu Asn Val Pro Leu Cys Lys Glu Asp Cys Glu Gln Trp Trp Glu
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 Asp Cys Arg Thr Ser Tyr Thr Cys Lys Ser Asn Trp His Lys Gly Trp
 145 150 155 160
 Asn Trp Thr Ser Gly Phe Asn Lys Cys Ala Val Gly Ala Ala Cys Gln
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 Pro Phe His Phe Tyr Phe Pro Thr Pro Thr Val Leu Cys Asn Glu Ile
 180 185 190
 Trp Thr His Ser Tyr Lys Val Ser Asn Tyr Ser Arg Gly Ser Gly Arg
 195 200 205
 Cys Ile Gln Met Trp Phe Asp Pro Ala Gln Gly Asn Pro Asn Glu Glu
 210 215 220
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<210> 112
 <211> 1104
 <212> DNA
 <213> Homo sapiens

<400> 112
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1104

<210> 113

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<213> Homo sapiens

<400> 113

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<211> 1331

<212> DNA

<213> Homo sapiens

<400> 114

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<211> 929

<212> DNA

<213> Homo sapiens

<400> 115

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<210> 116

<211> 858

<212> DNA

<213> Homo sapiens

<400> 116

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<210> 117

<211> 243

<212> PRT

<213> Homo sapiens

<400> 117

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Asn Val Cys Met Asn Ala Lys His His Lys Thr Gln Pro Ser Pro Glu
          35           40           45
Asp Glu Leu Tyr Gly Gln Cys Ser Pro Trp Lys Lys Asn Ala Cys Cys
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Thr Ala Ser Thr Ser Gln Glu Leu His Lys Asp Thr Ser Arg Leu Tyr
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Arg	Thr	Ser	Tyr	Thr	Cys	Lys	Ser	Asn	Trp	His	Lys	Gly	Trp	Asn	Trp
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Thr	Ser	Gly	Ile	Asn	Glu	Cys	Pro	Ala	Gly	Ala	Leu	Cys	Ser	Thr	Phe
			165						170					175	
Glu	Ser	Tyr	Phe	Pro	Thr	Pro	Ala	Ala	Leu	Cys	Glu	Gly	Leu	Trp	Ser
			180					185					190		
His	Ser	Phe	Lys	Val	Ser	Asn	Tyr	Ser	Arg	Gly	Ser	Gly	Arg	Cys	Ile
	195					200						205			
Gln	Met	Trp	Phe	Asp	Ser	Ala	Gln	Gly	Asn	Pro	Asn	Glu	Glu	Val	Ala
	210					215					220				
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Ile	Asp	Ser													

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 <211> 1362
 <212> DNA
 <213> Homo sapiens

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 <211> 453
 <212> PRT
 <213> Homo sapiens

<400> 119

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Glu	Tyr	Pro	Leu	Val	Asn	Val	Pro	Ser	His	Arg	Gly	Leu	Thr	Cys	Asn
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Arg	Ser	Ser	Thr	Arg	His	His	Glu	Gln	Pro	Glu	Thr	Ser	Asn	Met	Ser
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Ile	Cys	Thr	Asn	Leu	Ser	Ser	Arg	Trp	Thr	Val	Phe	Gln	Ser	Ser	Ile
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Val	Val	Thr	Leu	Ala	Val	Cys	Trp	Met	Pro	Asn	Gln	Ile	Arg	Arg	Ile
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Ala	Tyr	Met	Ile	Leu	Leu	Pro	Phe	Ser	Glu	Thr	Phe	Phe	Tyr	Leu	Ser
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Ser	Ala	Arg	Arg	Thr	Glu	Lys	Ile	Phe	Leu	Ser	Thr	Phe	Gln	Ser	Glu
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Ala	Glu	Pro	Gln	Ser	Lys	Ser	Gln	Ser	Leu	Ser	Leu	Glu	Ser	Leu	Glu
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<211> 2870
<212> DNA
<213> Homo sapiens

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tgctttttct ataaaactac ccataagcct ttaaccttta aagaaaaatg aaaaaggtta 2760
gtgttttggg gccgggggag gactgaccgc ttcataagcc agtacgtctg agctgagtat 2820
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<210> 121
<211> 403
<212> PRT
<213> Homo sapiens
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[illegible]

<210> 122
 <211> 1474
 <212> DNA
 <213> Homo sapiens

<400> 122
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 agtctcctca tatgtgcaag ctcgccctc ccttggaatc taaagcctcc tcagccttct 180
 gagtcagcct gaaaggaaca ggccgaactg ctgtatgggc tctactgcca gtgtgacctc 240
 accctctcca gtcacccctc ctcatgtcca gctatgagtt cctgcaactt cacacatgcc 300
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 ctcccttcca tgtatgtagt ggcaatgtgt ggaaactgca tctgtggtct catcgtaagg 420
 acggaacgca gcctgcacgc tccgatgtac ctctttctct gcattgctgc agccattgac 480
 ctggccttat ccacatccac catgcctaag atccttgccc ttttctgggt tgattcccga 540
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 agcacatcag tacttttctc tggctggaat agtaaactaa agtatggtac atctaccta 1380
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 aaaaccaaac atgcttataa cattaaaaaa aaaa 1474

<210> 123
 <211> 320
 <212> PRT
 <213> Homo sapiens

<400> 123
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 1 5 10 15
 Pro Gly Leu Glu Lys Ala His Phe Trp Val Gly Phe Pro Leu Leu Ser
 20 25 30
 Met Tyr Val Val Ala Met Cys Gly Asn Cys Ile Val Val Phe Ile Val
 35 40 45
 Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met
 50 55 60
 Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile
 65 70 75 80
 Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Ile Glu Ala Cys
 85 90 95
 Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr
 100 105 110
 Ile Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile Cys His Pro
 115 120 125
 Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly

130	135	140
Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Phe Pro Leu Pro Leu		
145	150	155
Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser		160
	165	170
Tyr Cys Val His Gln Asp Val Met Lys Leu Ala Tyr Ala Asp Thr Leu		175
	180	185
Pro Asn Val Val Tyr Gly Leu Thr Ala Ile Leu Leu Val Met Gly Val		190
	195	200
Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val		205
	210	215
Leu Gln Leu Pro Ser Lys Ser Glu Arg Ala Lys Ala Phe Gly Thr Cys		220
225	230	235
Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro Leu Ile Gly		240
	245	250
Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg		255
	260	265
Val Val Met Gly Asp Ile Tyr Leu Leu Pro Pro Val Ile Asn Pro		270
	275	280
Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala		285
	290	295
Met Phe Lys Ile Ser Cys Asp Lys Asp Leu Gln Ala Val Gly Gly Lys		300
305	310	315
		320

<210> 124

<211> 2205

<212> DNA

<213> Homo sapiens

<400> 124

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gccagacttc ggaacgggtg tcctgtctact cctgtctgggg ctctccagg acaagggcac 180
acaactggtt ccgttaagcc cctctctcgc tcagacgcca tggagctgga tctgtctcca 240
cctcatctta gcagctctcc ggaagacctt tggccagccc ctgggacccc tctgtggact 300
ccccggcccc ctgatacccc tctgacctgag gaggtaaaga ggtcccagcc tctcctcatc 360
ccaaccaccg gcaggaaact tcgagaggag gagaggcgtg ccacctccct cccctctatc 420
cccaaccctt tccctgagct ctgcagtcct cctcacaga gcccaattct cgggggcccc 480
tccagtgcaa gggggctgct cccccgcgat gccagccgcc cccatgtagt aaagggtgtac 540
agtgaggatg gggcctgcag gtctgtggag gtggcagcag gtgccacagc tcgccacgtg 600
tgtgaaatgc tggatgcagc agctcacgcc ttgagcgacg agacctgggg gctgggtggag 660
tgccaccccc acctagcact ggagcggggg ttggaggacc acgagtcctg ggtggaagtg 720
caggctgcct ggcccgtggg cggagatagc cgcttcgtct tccggaaaaa cttcgccaag 780
tacgaactgt tcaagagctc cccacactcc ctgttccag aaaaaatggt ctccagctgt 840
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cagggccgca agctctacgg gatgccact gacttcgggt tctgtgtcaa gccaacaag 1140
cttcgaaatg gacacaaggg gcttcggatc ttctgcagtg aagatgagca gagccgcacc 1200
tgctggctgg ctgccttcgg cctcttcaag tacgggggtg agctgtacaa gaattaccag 1260
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acccaactct ggttccacgg gcgcatttcc cgtgaggaga gccagcggct tattggacag 1560
cagggcttgg tagacggcct gttcctggtc cgggagagtc agcggaaccc ccagggcttt 1620

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gtcctctctt tgtgccacct gcagaaagtg aagcattatc tcatacctgcc gagcgaggag 1680
gaggggtcgcc tgtacttcag catggatgat ggccagaccc gcttcactga cctgctgcag 1740
ctcgtggagt tccaccagct gaaccgcggc atcctgccgt gcttgctgcg ccattgctgc 1800
acgcgggtgg ccctctgacc aggcctgga ctggctcatg cctcagcccg ccttcaggct 1860
gcccgcgcc cctccacca tccagtggac tctggggcgc ggccacaggg gacgggatga 1920
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tgggggcagc ccaggcgggt tcacgcccc cactttgtac agaccgagag gccagttgat 2160
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<210> 125

<211> 532

<212> PRT

<213> Homo sapiens

<400> 125

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Met Glu Leu Asp Leu Ser Pro Pro His Leu Ser Ser Ser Pro Glu Asp
1      5      10      15
Leu Trp Pro Ala Pro Gly Thr Pro Pro Gly Thr Pro Arg Pro Pro Asp
20      25      30
Thr Pro Leu Pro Glu Glu Val Lys Arg Ser Gln Pro Leu Leu Ile Pro
35      40      45
Thr Thr Gly Arg Lys Leu Arg Glu Glu Glu Arg Arg Ala Thr Ser Leu
50      55      60
Pro Ser Ile Pro Asn Pro Phe Pro Glu Leu Cys Ser Pro Pro Ser Gln
65      70      75      80
Ser Pro Ile Leu Gly Gly Pro Ser Ser Ala Arg Gly Leu Leu Pro Arg
85      90      95
Asp Ala Ser Arg Pro His Val Val Lys Val Tyr Ser Glu Asp Gly Ala
100     105     110
Cys Arg Ser Val Glu Val Ala Ala Gly Ala Thr Ala Arg His Val Cys
115     120     125
Glu Met Leu Val Gln Arg Ala His Ala Leu Ser Asp Glu Thr Trp Gly
130     135     140
Leu Val Glu Cys His Pro His Leu Ala Leu Glu Arg Gly Leu Glu Asp
145     150     155     160
His Glu Ser Val Val Glu Val Gln Ala Ala Trp Pro Val Gly Gly Asp
165     170     175
Ser Arg Phe Val Phe Arg Lys Asn Phe Ala Lys Tyr Glu Leu Phe Lys
180     185     190
Ser Ser Pro His Ser Leu Phe Pro Glu Lys Met Val Ser Ser Cys Leu
195     200     205
Asp Ala His Thr Gly Ile Ser His Glu Asp Leu Ile Gln Asn Phe Leu
210     215     220
Asn Ala Gly Ser Phe Pro Glu Ile Gln Gly Phe Leu Gln Leu Arg Gly
225     230     235     240
Ser Gly Arg Lys Leu Trp Lys Arg Phe Phe Cys Phe Leu Arg Arg Ser
245     250     255
Gly Leu Tyr Tyr Ser Thr Lys Gly Thr Ser Lys Asp Pro Arg His Leu
260     265     270
Gln Tyr Val Ala Asp Val Asn Glu Ser Asn Val Tyr Val Val Thr Gln
275     280     285
Gly Arg Lys Leu Tyr Gly Met Pro Thr Asp Phe Gly Phe Cys Val Lys
290     295     300
Pro Asn Lys Leu Arg Asn Gly His Lys Gly Leu Arg Ile Phe Cys Ser
305     310     315     320
Glu Asp Glu Gln Ser Arg Thr Cys Trp Leu Ala Ala Phe Arg Leu Phe

```

[illegible]

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<210> 126
<211> 1619
<212> DNA
<213> Homo sapiens
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<400>	126					
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ggctggggcc	ggcccaggag	cttccccagg	gctcccaccg	tccatggcgg	tgcgggggga	180
gcccgcattc	ccctgtcctt	caccacgcgg	agctgcccac	cccctggagg	gtcttggggg	240
tctggaagaa	gcagccccc	actaggcgga	aatgggaag	ccaccatgca	gaatctcaac	300
gaccgcctgg	ccctcctacc	ggagaagggt	cgcgccctgg	aggaggccaa	catgaagctg	360
gaaagccgca	tcctgaaatg	gcaccagcag	agagatcctg	gcagtaagaa	agattattcc	420
cagtatgagg	aaaacatcac	acacctgcag	gagcagatag	tggatggtaa	gatgaccaat	480
gctcagatta	ttcttctcat	tgacaatgcc	aggatggcag	tggatgactt	caacctcaag	540
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ctggaggata	tgagacaaga	atatagcgtt	ataataaaga	agaagcatcg	agacttggac	840
atttggtata	aagaacagtc	tgcagccatg	tcccaggagg	cagccagtcc	agccactgtg	900
cagagcagac	aaggtgacat	ccacgaactg	aagcgcacat	tccaggccct	ggagattgac	960
ctgcaggcac	agtacagcac	gaaatctgct	ttggaaaaca	tgttatccga	gacctagtct	1020
cggtactcct	gcaagctcca	ggacatgcaa	gagatcatct	cccactatga	ggaggaactg	1080
acgcagctac	gccacgaact	ggagcggcag	aacaatgaat	accaagtgtg	gctgggcatc	1140
aaaacccacc	tggagaagga	aatcaccacg	taaccgacgg	tcctggaggg	agagagttaa	1200
gtgacacggg	agaatatcaa	gtcgagcatg	aaagtgtctg	caactccaaa	gatcaaggcc	1260
ataacccgag	agaccatcaa	cgggaagatta	gttctttgtc	aagtgaatga	aatccaaaag	1320
cacgcattag	accaatgaaa	gtttccgcct	gttgtaaagt	ctattttccc	ccaaggaaaag	1380

137

tccttgcaca gacaccagtg agtgagttct aaaagatacc cttggaatta tcagactcag 1440
 aaacttttat tttttttttt ctgtaacagt ctcaccagac ttctcataat gctcttaata 1500
 tattgcactt ttctaataca agtgcgagtt tatgagggta aagctctact ttctactgc 1560
 agccttcaga ttctcatcat tttgcatcta tttttagtcc aataaaactc cgcactagc 1619

<210> 127

<211> 422

<212> PRT

<213> Homo sapiens

<400> 127

Met	Asn	Ser	Gly	His	Ser	Phe	Ser	Gln	Thr	Pro	Ser	Ala	Ser	Phe	His
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Gly	Ala	Gly	Gly	Gly	Trp	Gly	Arg	Pro	Arg	Ser	Phe	Pro	Arg	Ala	Pro
			20					25					30		
Thr	Val	His	Gly	Gly	Ala	Gly	Gly	Ala	Arg	Ile	Ser	Leu	Ser	Phe	Thr
		35					40					45			
Thr	Arg	Ser	Cys	Pro	Pro	Pro	Gly	Gly	Ser	Trp	Gly	Ser	Gly	Arg	Ser
	50					55					60				
Ser	Pro	Leu	Leu	Gly	Gly	Asn	Gly	Lys	Ala	Thr	Met	Gln	Asn	Leu	Asn
				70						75					80
Asp	Arg	Leu	Ala	Ser	Tyr	Leu	Glu	Lys	Val	Arg	Ala	Leu	Glu	Glu	Ala
			85						90					95	
Asn	Met	Lys	Leu	Glu	Ser	Arg	Ile	Leu	Lys	Trp	His	Gln	Gln	Arg	Asp
			100					105					110		
Pro	Gly	Ser	Lys	Lys	Asp	Tyr	Ser	Gln	Tyr	Glu	Glu	Asn	Ile	Thr	His
		115					120					125			
Leu	Gln	Glu	Gln	Ile	Val	Asp	Gly	Lys	Met	Thr	Asn	Ala	Gln	Ile	Ile
	130					135					140				
Leu	Leu	Ile	Asp	Asn	Ala	Arg	Met	Ala	Val	Asp	Asp	Phe	Asn	Leu	Lys
	145				150					155					160
Tyr	Glu	Asn	Glu	His	Ser	Phe	Lys	Lys	Asp	Leu	Glu	Ile	Glu	Val	Glu
				165					170					175	
Gly	Leu	Arg	Arg	Thr	Leu	Asp	Asn	Leu	Thr	Ile	Val	Thr	Thr	Asp	Leu
			180					185					190		
Glu	Gln	Glu	Val	Glu	Gly	Met	Arg	Lys	Glu	Leu	Ile	Leu	Met	Lys	Glu
		195					200					205			
His	His	Glu	Gln	Glu	Met	Glu	Glu	His	His	Val	Pro	Ser	Asp	Phe	Asn
	210					215					220				
Val	Asn	Val	Lys	Val	Asp	Thr	Gly	Pro	Arg	Glu	Asp	Leu	Ile	Lys	Val
	225				230					235					240
Leu	Glu	Asp	Met	Arg	Gln	Glu	Tyr	Glu	Leu	Ile	Ile	Lys	Lys	Lys	His
			245						250					255	
Arg	Asp	Leu	Asp	Thr	Trp	Tyr	Lys	Glu	Gln	Ser	Ala	Ala	Met	Ser	Gln
		260						265					270		
Glu	Ala	Ala	Ser	Pro	Ala	Thr	Val	Gln	Ser	Arg	Gln	Gly	Asp	Ile	His
		275					280					285			
Glu	Leu	Lys	Arg	Thr	Phe	Gln	Ala	Leu	Glu	Ile	Asp	Leu	Gln	Ala	Gln
	290					295					300				
Tyr	Ser	Thr	Lys	Ser	Ala	Leu	Glu	Asn	Met	Leu	Ser	Glu	Thr	Gln	Ser
	305				310					315					320
Arg	Tyr	Ser	Cys	Lys	Leu	Gln	Asp	Met	Gln	Glu	Ile	Ile	Ser	His	Tyr
			325						330					335	
Glu	Glu	Glu	Leu	Thr	Gln	Leu	Arg	His	Glu	Leu	Glu	Arg	Gln	Asn	Asn
			340					345					350		
Glu	Tyr	Gln	Val	Leu	Leu	Gly	Ile	Lys	Thr	His	Leu	Glu	Lys	Glu	Ile
		355				360						365			
Thr	Thr	Tyr	Arg	Arg	Leu	Leu	Glu	Gly	Glu	Ser	Glu	Gly	Thr	Arg	Glu

370		375		380
Glu Ser Lys Ser Ser Met Lys Val Ser Ala Thr	Pro Lys Ile Lys Ala			
385	390	395	400	
Ile Thr Gln Glu Thr Ile Asn Gly Arg Leu Val	Leu Cys Gln Val Asn			
	405	410	415	
Glu Ile Gln Lys His Ala				
420				

<210> 128
 <211> 1359
 <212> DNA
 <213> Homo sapiens

<400> 128
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 aatgcttttat tttctaaata tccagcctca agttcggttt tcgctaccgg agccttccca 180
 gaacaaactt cttgtgcgtt tgcttccaac cccagcgcc cgggctatgg agcgggttcg 240
 ggcgcttcct tcgccggctc gatgcagggc ttgtaccccg gcgggggggg catggcgggc 300
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 cactgcgcgc cttttgagca gaacctctcc ggggtgtgtc ccggcgactc cgccaaggcg 420
 gcgggcgcca aggagcagag ggactcggac ttggcgggcc agagtaactt ccgatctac 480
 ccctcgatgc gaagctcagg aactgaccgc aaacgaggcc gccagacctc caccgctac 540
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 cggcgcatga agtggaaaaa ggagaacaag accgcgggcc cggggaccac cggccaagac 720
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 catgagaaag ggagacgaag agaagcccag ctctgggaac tgaatcagga aactcaaadc 840
 gaatagggaa gtaaaaaaac aaaaacaaaa acaaaaaaaa acaaaaaaaa accctattta 900
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 agcagcgga ccaaggggccc ttaggagacc ccaaaaccta ccactcgcgt gttccccaag 1260
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<210> 129
 <211> 217
 <212> PRT
 <213> Homo sapiens

<400> 129
 Met Ser Ser Leu Tyr Tyr Ala Asn Ala Leu Phe Ser Lys Tyr Pro Ala
 1 5 10 15
 Ser Ser Ser Val Phe Ala Thr Gly Ala Phe Pro Glu Gln Thr Ser Cys
 20 25 30
 Ala Phe Ala Ser Asn Pro Gln Arg Pro Gly Tyr Gly Ala Gly Ser Gly
 35 40 45
 Ala Ser Phe Ala Gly Ser Met Gln Gly Leu Tyr Pro Gly Gly Gly Gly
 50 55 60
 Met Ala Gly Gln Ser Ala Ala Gly Val Tyr Ala Gly Tyr Gly Leu
 65 70 75 80
 Glu Pro Ser Ser Phe Asn Met His Cys Ala Pro Phe Glu Gln Asn Leu
 85 90 95
 Ser Gly Val Cys Pro Gly Asp Ser Ala Lys Ala Ala Gly Ala Lys Glu

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<210> 130
<211> 1257
<212> DNA
<213> Homo sapiens
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<210> 131
<211> 278
<212> PRT
<213> Homo sapiens
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<400> 131																
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1				5					10					15		
Val	Pro	Leu	Leu	Gly	Leu	Leu	Arg	Leu	Gln	Leu	Arg	Ala	Ala	Arg	Gln	
			20					25					30			
Pro	Gly	Ala	Met	Arg	Pro	Gln	Gly	Pro	Ala	Ala	Ser	Pro	Gln	Arg	Leu	
		35					40					45				
Arg	Gly	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Gln	Leu	Pro	Ala	Pro	Ser	Ser	

140

50	55	60
Ala Ser Glu Ile Pro Lys	Gly Lys Gln Lys Ala	Gln Leu Arg Gln Arg
65	70	75
Glu Val Val Asp Leu Tyr	Asn Gly Met Cys Leu	Gln Gly Pro Ala Gly
85	90	95
Val Pro Gly Arg Asp Gly	Ser Pro Gly Ala Asn	Gly Ile Pro Gly Thr
100	105	110
Pro Gly Ile Pro Gly Arg	Asp Gly Phe Lys Gly	Glu Lys Gly Glu Cys
115	120	125
Leu Arg Glu Ser Phe Glu	Glu Ser Trp Thr Pro	Asn Tyr Lys Gln Cys
130	135	140
Ser Trp Ser Ser Leu Asn	Tyr Gly Ile Asp Leu	Gly Lys Ile Ala Glu
145	150	155
Cys Thr Phe Thr Lys Met	Arg Ser Asn Ser Ala	Leu Arg Val Leu Phe
165	170	175
Ser Gly Ser Leu Arg Leu	Lys Cys Arg Asn Ala	Cys Cys Gln Arg Trp
180	185	190
Tyr Phe Thr Phe Asn Gly	Ala Glu Cys Ser Gly	Pro Leu Pro Ile Glu
195	200	205
Ala Ile Ile Tyr Leu Asp	Gln Gly Ser Pro Glu	Met Asn Ser Thr Ile
210	215	220
Asn Ile His Arg Thr Ser	Ser Val Glu Gly Leu	Cys Glu Gly Ile Gly
225	230	235
Ala Gly Leu Val Asp Val	Ala Ile Trp Val Gly	Thr Cys Ser Asp Tyr
245	250	255
Pro Lys Gly Asp Ala Ser	Thr Gly Trp Asn Ser	Val Ser Arg Ile Ile
260	265	270
Ile Glu Glu Leu Pro Lys		
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 <213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Gly Arg Asp Gly Phe Lys Gly Glu Lys Gly Glu Cys Leu Arg Glu Ser
 50 55 60
 Phe Glu Glu Ser Trp Thr Pro Asn Tyr Lys Gln Cys Ser Trp Ser Ser
 65 70 75 80
 Leu Asn Tyr Gly Ile Asp Leu Gly Lys Ile Ala Glu Cys Thr Phe Thr
 85 90 95
 Lys Met Arg Ser Asn Ser Ala Leu Arg Val Leu Phe Ser Gly Ser Leu
 100 105 110
 Arg Leu Lys Cys Arg Asn Ala Cys Cys Gln Arg Trp Tyr Phe Thr Phe
 115 120 125
 Asn Gly Ala Glu Cys Ser Gly Pro Leu Pro Ile Glu Ala Ile Ile Tyr
 130 135 140
 Leu Asp Gln Gly Ser Pro Glu Met Asn Ser Thr Ile Asn Ile His Arg
 145 150 155 160
 Thr Ser Ser Val Glu Gly Leu Cys Glu Gly Ile Gly Ala Gly Leu Val
 165 170 175
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 Ala Ser Thr Gly Trp Asn Ser Val Ser Arg Ile Ile Ile Glu Glu Leu
 195 200 205
 Pro Lys
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 <213> Homo sapiens

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142

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<211> 243

<212> PRT

<213> Homo sapiens

<400> 135

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 20          25          30
Ile Pro Lys Gly Lys Gln Lys Ala Gln Leu Arg Gln Arg Glu Val Val
 35          40          45
Asp Leu Tyr Asn Gly Met Cys Leu Gln Gly Pro Ala Gly Val Pro Gly
 50          55          60
Arg Asp Gly Ser Pro Gly Ala Asn Gly Ile Pro Gly Thr Pro Gly Ile
 65          70          75          80
Pro Gly Arg Asp Gly Phe Lys Gly Glu Lys Gly Glu Cys Leu Arg Glu
 85          90          95
Ser Phe Glu Glu Ser Trp Thr Pro Asn Tyr Lys Gln Cys Ser Trp Ser
100          105          110
Ser Leu Asn Tyr Gly Ile Asp Leu Gly Lys Ile Ala Glu Cys Thr Phe
115          120          125
Thr Lys Met Arg Ser Asn Ser Ala Leu Arg Val Leu Phe Ser Gly Ser
130          135          140
Leu Arg Leu Lys Cys Arg Asn Ala Cys Cys Gln Arg Trp Tyr Phe Thr
145          150          155          160
Phe Asn Gly Ala Glu Cys Ser Gly Pro Leu Pro Ile Glu Ala Ile Ile
165          170          175
Tyr Leu Asp Gln Gly Ser Pro Glu Met Asn Ser Thr Ile Asn Ile His
180          185          190
Arg Thr Ser Ser Val Glu Gly Leu Cys Glu Gly Ile Gly Ala Gly Leu
195          200          205
Val Asp Val Ala Ile Trp Val Gly Thr Cys Ser Asp Tyr Pro Lys Gly
210          215          220
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<210> 136

<211> 5519

<212> DNA

<213> Homo sapiens

<400> 136

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<210> 137

<211> 765

<212> PRT

<213> Homo sapiens

<400> 137

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          35           40           45
Lys Thr Lys Leu Asp Thr Leu Ala Thr Gly His Leu Phe Gln Glu Val
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Arg Cys Met Lys Leu Val Gln His Pro Asn Ile Val Arg Leu Tyr Glu
65           70           75           80
Val Ile Asp Thr Gln Thr Lys Leu Tyr Leu Ile Leu Glu Leu Gly Asp
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Glu Gly Asp Met Phe Asp Tyr Ile Met Lys His Glu Glu Gly Leu Asn
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Glu Asp Leu Pro Lys Lys Tyr Phe Ala Gln Ile Val His Ala Ile Ser
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Tyr Cys His Lys Leu His Val Val His Arg Asp Leu Lys Pro Glu Asn
          130          135          140
Val Val Phe Phe Glu Lys Gln Gly Leu Val Lys Leu Thr Asp Phe Gly
145          150          155          160
Phe Ser Asn Lys Phe Gln Pro Gly Lys Lys Leu Thr Thr Ser Cys Gly

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Ile	Ser	Ser	Thr	Gly	Asn	Ala	Gly	Gln	Val	Pro	Ala	Val	Gly	Gly	Ile
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Lys	Phe	Phe	Ser	Asp	His	Met	Ala	Asp	Thr	Thr	Thr	Glu	Leu	Glu	Arg
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 <211> 2029
 <212> DNA
 <213> Homo sapiens

<400> 138

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2029

<210> 139

<211> 379

<212> PRT

<213> Homo sapiens

<400> 139

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Ala	Pro	Ser 35	Gln	Asn	Ile	Phe	Phe 40	Ser	Pro	Val	Ser	Ile 45	Ser	Met	Ser
Leu	Ala 50	Met	Leu	Ser	Leu	Gly 55	Ala	Gly	Ser	Ser	Thr 60	Lys	Met	Gln	Ile
Leu 65	Glu	Gly	Leu	Gly 70	Leu	Asn	Leu	Gln	Lys 75	Ser	Ser	Glu	Lys	Glu	Leu 80
His	Arg	Gly	Phe 85	Gln	Gln	Leu	Leu	Gln	Glu 90	Leu	Asn	Gln	Pro	Arg	Asp
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Asp	Thr 130	Phe	Pro	Thr	Asn	Phe 135	Arg	Asp	Ser	Ala	Gly 140	Ala	Met	Lys	Gln
Ile 145	Asn	Asp	Tyr	Val 150	Ala	Lys	Gln	Thr	Lys	Gly 155	Lys	Ile	Val	Asp	Leu 160
Leu	Lys	Asn	Leu 165	Asp	Ser	Asn	Ala	Val	Val 170	Ile	Met	Val	Asn	Tyr	Ile
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Cys 225	Arg	Val	Val	Gly 230	Val	Pro	Tyr	Gln	Gly	Asn 235	Ala	Thr	Ala	Leu	Phe 240
Ile	Leu	Pro	Ser 245	Glu	Gly	Lys	Met	Gln	Gln 250	Val	Glu	Asn	Gly	Leu	Ser
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Glu	Leu 275	Tyr	Leu	Pro	Lys	Phe	Ser 280	Ile	Glu	Gly	Ser	Tyr 285	Gln	Leu	Glu
Lys 290	Val	Leu	Pro	Ser	Leu	Gly 295	Ile	Ser	Asn	Val	Phe 300	Thr	Ser	His	Ala
Asp 305	Leu	Ser	Gly	Ile 310	Ser	Asn	His	Ser	Asn	Ile 315	Gln	Val	Ser	Glu	Met 320
Val	His 325	Lys	Ala	Val	Val	Glu	Val	Asp	Glu 330	Ser	Gly	Thr	Arg	Ala	Ala
Ala	Ala	Thr 340	Gly	Thr	Ile	Phe	Thr 345	Phe	Arg	Ser	Ala	Arg	Leu 350	Asn	Ser
Gln	Arg 355	Leu	Val	Phe	Asn	Arg	Pro 360	Phe	Leu	Met	Phe	Ile 365	Val	Asp	Asn
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 <211> 2058
 <212> DNA
 <213> Homo sapiens

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<210> 141
 <211> 413
 <212> PRT
 <213> Homo sapiens

<400> 141
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 35 40 45
 Gln Lys Lys Asn Asp Thr Thr Glu Ile Glu Thr Leu Leu Leu Asn Thr
 50 55 60
 Ala Pro Lys Ile Ile Asp Glu Gln Leu Val Cys Arg Leu Ser Lys Thr
 65 70 75 80

149

Asp Ile Phe Ile Ile Cys Arg Asp Asn Lys Ile Tyr Leu Asp Lys Met
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 100 105 110
 Glu Cys Glu Val Phe Arg Val Glu Gly Ile Lys Asp Asn Leu Asp Asp
 115 120 125
 Ile Lys Arg Ile Ile Lys Ala Arg Glu His Arg Asn Arg Leu Leu Ala
 130 135 140
 Asp Ile Arg Asp Tyr Arg Pro Tyr Ala Asp Leu Val Ser Glu Ile Arg
 145 150 155 160
 Ile Leu Leu Val Gly Pro Val Gly Ser Gly Lys Ser Ser Phe Phe Asn
 165 170 175
 Ser Val Lys Ser Ile Phe His Gly His Val Thr Gly Gln Ala Val Val
 180 185 190
 Gly Ser Asp Thr Thr Ser Ile Thr Glu Arg Tyr Arg Ile Tyr Ser Val
 195 200 205
 Lys Asp Gly Lys Asn Gly Lys Ser Leu Pro Phe Met Leu Cys Asp Thr
 210 215 220
 Met Gly Leu Asp Gly Ala Glu Gly Ala Gly Leu Cys Met Asp Asp Ile
 225 230 235 240
 Pro His Ile Leu Lys Gly Cys Met Pro Asp Arg Tyr Gln Phe Asn Ser
 245 250 255
 Arg Lys Pro Ile Thr Pro Glu His Ser Thr Phe Ile Thr Ser Pro Ser
 260 265 270
 Leu Lys Asp Arg Ile His Cys Val Ala Tyr Val Leu Asp Ile Asn Ser
 275 280 285
 Ile Asp Asn Leu Tyr Ser Lys Met Leu Ala Lys Val Lys Gln Val His
 290 295 300
 Lys Glu Val Leu Asn Cys Gly Ile Ala Tyr Val Ala Leu Leu Thr Lys
 305 310 315 320
 Val Asp Asp Cys Ser Glu Val Leu Gln Asp Asn Phe Leu Asn Met Ser
 325 330 335
 Arg Ser Met Thr Ser Gln Ser Arg Val Met Asn Val His Lys Met Leu
 340 345 350
 Gly Ile Pro Ile Ser Asn Ile Leu Met Val Gly Asn Tyr Ala Ser Asp
 355 360 365
 Leu Glu Leu Asp Pro Met Lys Asp Ile Leu Ile Leu Ser Ala Leu Arg
 370 375 380
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<210> 142

<211> 1032

<212> DNA

<213> Homo sapiens

<400> 142

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150

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<210> 143

<211> 303

<212> PRT

<213> Homo sapiens

<400> 143

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Ala Ala Val Gln Ala Ser Pro Leu Gln Ala Leu Asp Phe Phe Gly Asn
35      40      45
Gly Pro Pro Val Asn Tyr Lys Thr Gly Asn Leu Tyr Leu Arg Gly Pro
50      55      60
Leu Lys Lys Ser Asn Ala Pro Leu Val Asn Val Thr Leu Tyr Tyr Glu
65      70      75      80
Ala Leu Cys Gly Gly Cys Arg Ala Phe Leu Ile Arg Glu Leu Phe Pro
85      90      95
Thr Trp Leu Leu Val Met Glu Ile Leu Asn Val Thr Ser Val Pro Tyr
100     105     110
Gly Asn Ala Gln Glu Gln Asn Val Ser Gly Arg Trp Glu Phe Lys Cys
115     120     125
Gln Leu Gly Glu Glu Glu Cys Lys Phe Asn Lys Val Glu Ala Cys Val
130     135     140
Leu Asp Glu Leu Asp Met Glu Leu Ala Phe Leu Thr Met Ser Gly Met
145     150     155     160
Ala Trp Lys Ser Leu Arg Thr Trp Arg Glu Val Cys His Tyr Ala Cys
165     170     175
Ser Ser Thr Pro Gln Gly Cys Arg Gln Asn Tyr His Gly Val Cys Asn
180     185     190
Gly Gly Pro Arg His Ala Ala His Ala Arg Gln Arg Pro Ala Asp Arg
195     200     205
Cys Ser Pro Ala Thr Ala Arg Val Cys Ala Leu Gly His Arg Gln Trp
210     215     220
Glu Thr Leu Gly Arg Ser Asp Pro Ala Pro Tyr Pro Cys Leu Pro Val
225     230     235     240
Val Pro Gly Gln Glu Ala Gly Cys Leu Pro Phe Leu Asn Gln Leu Pro
245     250     255
Pro Glu Cys Leu Leu Arg Val Leu Ala Gly Gly Leu Arg Arg Ala His
260     265     270
Gly Arg Arg Val Gly Thr Arg Leu Pro Ala Phe Phe Ser Asp Pro Asp
275     280     285
Pro Arg His Leu Leu Leu Thr Asn Trp Lys Ile Leu Cys Ile Pro
290     295     300

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<210> 144

<211> 1356

<212> DNA

<213> Homo sapiens

<400> 144

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<210> 145

<211> 180

<212> PRT

<213> Homo sapiens

<400> 145

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Cys Gly Gly Glu Leu Val Asp Thr Leu Gln Phe Val Cys Gly Asp Arg
35 40 45
Gly Phe Tyr Phe Ser Arg Pro Ala Ser Arg Val Ser Arg Arg Ser Arg
50 55 60
Gly Ile Val Glu Glu Cys Phe Arg Ser Cys Asp Leu Ala Leu Leu
65 70 75 80
Glu Thr Tyr Cys Ala Thr Pro Ala Lys Ser Glu Arg Asp Val Ser Thr
85 90 95
Pro Pro Thr Val Leu Pro Asp Asn Phe Pro Arg Tyr Pro Val Gly Lys
100 105 110
Phe Phe Gln Tyr Asp Thr Trp Lys Gln Ser Thr Gln Arg Leu Arg Arg
115 120 125
Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly His Val Leu Ala Lys
130 135 140
Glu Leu Glu Ala Phe Arg Glu Ala Lys Arg His Arg Pro Leu Ile Ala
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Ser Asn Arg Lys

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180

<210> 146
 <211> 3667
 <212> DNA
 <213> Homo sapiens

<400> 146
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<210> 147

<211> 556

<212> PRT

<213> Homo sapiens

<400> 147

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Gln Val Leu Leu Lys Ser Gly Tyr Ala Phe Val Asp Tyr Pro Asp Gln
          35          40          45
Asn Trp Ala Ile Arg Ala Ile Glu Thr Leu Ser Gly Lys Val Glu Leu
          50          55          60
His Gly Lys Ile Met Glu Val Asp Tyr Ser Val Ser Lys Lys Leu Arg
65          70          75          80
Ser Arg Lys Ile Gln Ile Arg Asn Ile Pro Pro His Leu Gln Trp Glu
          85          90          95
Val Leu Asp Gly Leu Leu Ala Gln Tyr Gly Thr Val Glu Asn Val Glu
          100         105         110
Gln Val Asn Thr Asp Thr Glu Thr Ala Val Val Asn Val Thr Tyr Ala
          115         120         125
Thr Arg Glu Glu Ala Lys Ile Ala Met Glu Lys Leu Ser Gly His Gln
130         135         140
Phe Glu Asn Tyr Ser Phe Lys Ile Ser Tyr Ile Pro Asp Glu Glu Val
145         150         155         160
Ser Ser Pro Ser Pro Pro Gln Arg Ala Gln Arg Gly Asp His Ser Ser
          165         170         175
Arg Glu Gln Gly His Ala Pro Gly Gly Thr Ser Gln Ala Arg Gln Ile
          180         185         190
Asp Phe Pro Leu Arg Ile Leu Val Pro Thr Gln Phe Val Gly Ala Ile
          195         200         205
Ile Gly Lys Glu Gly Leu Thr Ile Lys Asn Ile Thr Lys Gln Thr Gln
210         215         220
Ser Arg Val Asp Ile His Arg Lys Glu Asn Ser Gly Ala Ala Glu Lys
225         230         235         240
Pro Val Thr Ile His Ala Thr Pro Glu Gly Thr Ser Glu Ala Cys Arg
          245         250         255
Met Ile Leu Glu Ile Met Gln Lys Glu Ala Asp Glu Thr Lys Leu Ala
          260         265         270
Glu Glu Ile Pro Leu Lys Ile Leu Ala His Asn Gly Leu Val Gly Arg
          275         280         285
Leu Ile Gly Lys Glu Gly Arg Asn Leu Lys Lys Ile Glu His Glu Thr
290         295         300

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Gly	Thr	Lys	Ile	Thr	Ile	Ser	Ser	Leu	Gln	Asp	Leu	Ser	Ile	Tyr	Asn
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Pro	Glu	Arg	Thr	Ile	Thr	Val	Lys	Gly	Thr	Val	Glu	Ala	Cys	Ala	Ser
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Ala	Glu	Ile	Glu	Ile	Met	Lys	Lys	Leu	Arg	Glu	Ala	Phe	Glu	Asn	Asp
			340						345					350	
Met	Leu	Ala	Val	Asn	Thr	His	Ser	Gly	Tyr	Phe	Ser	Ser	Leu	Tyr	Pro
		355					360					365			
His	His	Gln	Phe	Gly	Pro	Phe	Pro	His	His	His	Ser	Tyr	Pro	Glu	Gln
	370						375					380			
Glu	Ile	Val	Asn	Leu	Phe	Ile	Pro	Thr	Gln	Ala	Val	Gly	Ala	Ile	Ile
385						390				395					400
Gly	Lys	Lys	Gly	Ala	His	Ile	Lys	Gln	Leu	Ala	Arg	Phe	Ala	Gly	Ala
				405					410					415	
Ser	Ile	Lys	Ile	Ala	Pro	Ala	Glu	Gly	Pro	Asp	Val	Ser	Glu	Arg	Met
			420					425					430		
Val	Ile	Ile	Thr	Gly	Pro	Pro	Glu	Ala	Gln	Phe	Lys	Ala	Gln	Gly	Arg
		435					440					445			
Ile	Phe	Gly	Lys	Leu	Lys	Glu	Glu	Asn	Phe	Phe	Asn	Pro	Lys	Glu	Glu
	450					455					460				
Val	Lys	Leu	Glu	Ala	His	Ile	Arg	Val	Pro	Ser	Ser	Thr	Ala	Gly	Arg
465					470					475					480
Val	Ile	Gly	Lys	Gly	Gly	Lys	Thr	Val	Asn	Glu	Leu	Gln	Asn	Leu	Thr
				485					490					495	
Ser	Ala	Glu	Val	Ile	Val	Pro	Arg	Asp	Gln	Thr	Pro	Asp	Glu	Asn	Glu
			500					505					510		
Glu	Val	Ile	Val	Arg	Ile	Ile	Gly	His	Phe	Phe	Ala	Ser	Gln	Thr	Ala
		515					520					525			
Gln	Arg	Lys	Ile	Arg	Glu	Ile	Val	Gln	Gln	Val	Lys	Gln	Gln	Glu	Gln
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Lys	Tyr	Pro	Gln	Gly	Val	Ala	Ser	Gln	Arg	Ser	Lys				
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<210> 148

<211> 1475

<212> DNA

<213> Homo sapiens

<400> 148

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155

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<210> 149

<211> 403

<212> PRT

<213> Homo sapiens

<400> 149

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Pro Asp Phe Tyr Asn Asp Trp Met Phe Ile Ala Lys His Leu Pro Asp
      35          40          45
Leu Ile Glu Ser Gly Gln Leu Arg Glu Arg Val Glu Lys Leu Asn Met
      50          55          60
Leu Ser Ile Asp His Leu Thr Asp His Lys Ser Gln Arg Leu Ala Arg
      65          70          75          80
Leu Val Leu Gly Cys Ile Thr Met Ala Tyr Val Trp Gly Lys Gly His
      85          90          95
Gly Asp Val Arg Lys Val Leu Pro Arg Asn Ile Ala Val Pro Tyr Cys
      100          105          110
Gln Leu Ser Lys Lys Leu Glu Leu Pro Pro Ile Leu Val Tyr Ala Asp
      115          120          125
Cys Val Leu Ala Asn Trp Lys Lys Lys Asp Pro Asn Lys Pro Leu Thr
      130          135          140
Tyr Glu Asn Met Asp Val Leu Phe Ser Phe Arg Asp Gly Asp Cys Ser
      145          150          155          160
Lys Gly Phe Phe Leu Val Ser Leu Leu Val Glu Ile Ala Ala Ala Ser
      165          170          175
Ala Ile Lys Val Ile Pro Thr Val Phe Lys Ala Met Gln Met Gln Glu
      180          185          190
Arg Asp Thr Leu Leu Lys Ala Leu Leu Glu Ile Ala Ser Cys Leu Glu
      195          200          205
Lys Ala Leu Gln Val Phe His Gln Ile His Asp His Val Asn Pro Lys
      210          215          220
Ala Phe Phe Ser Val Leu Arg Ile Tyr Leu Ser Gly Trp Lys Gly Asn
      225          230          235          240
Pro Gln Leu Ser Asp Gly Leu Val Tyr Glu Gly Phe Trp Glu Asp Pro
      245          250          255
Lys Glu Phe Ala Gly Gly Ser Ala Gly Gln Ser Ser Val Phe Gln Cys
      260          265          270
Phe Asp Val Leu Leu Gly Ile Gln Gln Thr Ala Gly Gly Gly His Ala
      275          280          285
Ala Gln Phe Leu Gln Asp Met Arg Arg Tyr Met Pro Pro Ala His Arg
      290          295          300
Asn Phe Leu Cys Ser Leu Glu Ser Asn Pro Ser Val Arg Glu Phe Val
      305          310          315          320
Leu Ser Lys Gly Asp Ala Gly Leu Arg Glu Ala Tyr Asp Ala Cys Val
      325          330          335
Lys Ala Leu Val Ser Leu Arg Ser Tyr His Leu Gln Ile Val Thr Lys
      340          345          350

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Tyr Ile Leu Ile Pro Ala Ser Gln Gln Pro Lys Glu Asn Lys Thr Ser
 355 360 365
 Glu Asp Pro Ser Lys Leu Glu Ala Lys Gly Thr Gly Gly Thr Asp Leu
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 Met Asn Phe Leu Lys Thr Val Arg Ser Thr Thr Glu Lys Ser Leu Leu
 385 390 395 400
 Lys Glu Gly

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 <211> 2129
 <212> DNA
 <213> Homo sapiens

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 aatccacgct ggcgttgacg ctaggccagc ggctcggcgg tgagatcgct agcgtgact 180
 ccatgcaggt ctatgaaggc ctagacatca tcaccaacaa ggtttctgcc caagagcaga 240
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<210> 151
 <211> 465
 <212> PRT
 <213> Homo sapiens

<400> 151

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			20					25					30		
Gly	Thr	Ser	Thr	Leu	Ala	Leu	Gln	Leu	Gly	Gln	Arg	Leu	Gly	Gly	Glu
			35				40					45			
Ile	Val	Ser	Ala	Asp	Ser	Met	Gln	Val	Tyr	Glu	Gly	Leu	Asp	Ile	Ile
	50				55						60				
Thr	Asn	Lys	Val	Ser	Ala	Gln	Glu	Gln	Arg	Ile	Cys	Arg	His	His	Met
65					70					75					80
Ile	Ser	Phe	Val	Asp	Pro	Leu	Val	Thr	Asn	Tyr	Thr	Val	Val	Asp	Phe
				85					90					95	
Arg	Asn	Arg	Ala	Thr	Ala	Leu	Ile	Glu	Asp	Ile	Phe	Ala	Arg	Asp	Lys
			100					105					110		
Ile	Pro	Ile	Val	Val	Gly	Gly	Thr	Asn	Tyr	Tyr	Ile	Glu	Ser	Leu	Leu
	115						120					125			
Trp	Lys	Val	Leu	Val	Asn	Thr	Lys	Pro	Gln	Glu	Met	Gly	Thr	Glu	Lys
	130					135					140				
Val	Ile	Asp	Arg	Lys	Val	Glu	Leu	Glu	Lys	Glu	Asp	Gly	Leu	Val	Leu
145					150					155					160
His	Lys	Arg	Leu	Ser	Gln	Val	Asp	Pro	Glu	Met	Ala	Ala	Lys	Leu	His
				165					170					175	
Pro	His	Asp	Lys	Arg	Lys	Val	Ala	Arg	Ser	Leu	Gln	Val	Phe	Glu	Glu
			180					185					190		
Thr	Gly	Ile	Ser	His	Ser	Glu	Phe	Leu	His	Arg	Gln	His	Thr	Glu	Glu
	195					200						205			
Gly	Gly	Gly	Pro	Leu	Gly	Gly	Pro	Leu	Lys	Phe	Ser	Asn	Pro	Cys	Ile
	210					215					220				
Leu	Trp	Leu	His	Ala	Asp	Gln	Ala	Val	Leu	Asp	Glu	Arg	Leu	Asp	Lys
225					230					235					240
Arg	Val	Asp	Asp	Met	Leu	Ala	Ala	Gly	Leu	Leu	Glu	Glu	Leu	Arg	Asp
				245					250					255	
Phe	His	Arg	Arg	Tyr	Asn	Gln	Lys	Asn	Val	Ser	Glu	Asn	Ser	Gln	Asp
			260					265					270		
Tyr	Gln	His	Gly	Ile	Phe	Gln	Ser	Ile	Gly	Phe	Lys	Glu	Phe	His	Glu
	275					280						285			
Tyr	Leu	Ile	Thr	Glu	Gly	Lys	Cys	Thr	Leu	Glu	Thr	Ser	Asn	Gln	Leu
	290					295					300				
Leu	Lys	Lys	Gly	Ile	Glu	Ala	Leu	Lys	Gln	Val	Thr	Lys	Arg	Tyr	Ala
305					310					315					320
Arg	Lys	Gln	Asn	Arg	Trp	Val	Lys	Asn	Arg	Phe	Leu	Ser	Arg	Pro	Gly
			325						330					335	
Pro	Ile	Val	Pro	Pro	Val	Tyr	Gly	Leu	Glu	Val	Ser	Asp	Val	Ser	Lys
			340					345					350		
Trp	Glu	Glu	Ser	Val	Leu	Glu	Pro	Ala	Leu	Glu	Ile	Val	Gln	Ser	Phe
	355						360					365			
Ile	Gln	Gly	His	Lys	Pro	Thr	Ala	Thr	Pro	Ile	Lys	Met	Pro	Tyr	Asn
	370					375					380				
Glu	Ala	Glu	Asn	Lys	Arg	Ser	Tyr	His	Leu	Cys	Asp	Leu	Cys	Asp	Arg
385					390					395					400
Ile	Ile	Ile	Gly	Asp	Arg	Glu	Trp	Ala	Ala	His	Ile	Lys	Ser	Lys	Ser
			405						410					415	
His	Leu	Asn	Gln	Leu	Lys	Lys	Arg	Arg	Arg	Leu	Asp	Ser	Asp	Ala	Val
			420					425					430		
Asn	Thr	Ile	Glu	Ser	Gln	Ser	Val	Ser	Pro	Asp	His	Asn	Lys	Glu	Pro
	435						440					445			
Lys	Glu	Lys	Gly	Ser	Pro	Gly	Gln	Asn	Asp	Gln	Glu	Leu	Lys	Cys	Ser

450
Val
465

<210> 152
<211> 2129
<212> DNA
<213> Homo sapiens

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<211> 467
<212> PRT
<213> Homo sapiens

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 35 40 45
 Gly Glu Ile Val Ser Ala Asp Ser Met Gln Val Tyr Glu Gly Leu Asp
 50 55 60
 Ile Ile Thr Asn Lys Val Ser Ala Gln Glu Gln Arg Ile Cys Arg His
 65 70 75 80
 His Met Ile Ser Phe Val Asp Pro Leu Val Thr Asn Tyr Thr Val Val
 85 90 95
 Asp Phe Arg Asn Arg Ala Thr Ala Leu Ile Glu Asp Ile Phe Ala Arg
 100 105 110
 Asp Lys Ile Pro Ile Val Val Gly Gly Thr Asn Tyr Tyr Ile Glu Ser
 115 120 125
 Leu Leu Trp Lys Val Leu Val Asn Thr Lys Pro Gln Glu Met Gly Thr
 130 135 140
 Glu Lys Val Ile Asp Arg Lys Val Glu Leu Glu Lys Glu Asp Gly Leu
 145 150 155 160
 Val Leu His Lys Arg Leu Ser Gln Val Asp Pro Glu Met Ala Ala Lys
 165 170 175
 Leu His Pro His Asp Lys Arg Lys Val Ala Arg Ser Leu Gln Val Phe
 180 185 190
 Glu Glu Thr Gly Ile Ser His Ser Glu Phe Leu His Arg Gln His Thr
 195 200 205
 Glu Glu Gly Gly Gly Pro Leu Gly Gly Pro Leu Lys Phe Ser Asn Pro
 210 215 220
 Cys Ile Leu Trp Leu His Ala Asp Gln Ala Val Leu Asp Glu Arg Leu
 225 230 235 240
 Asp Lys Arg Val Asp Asp Met Leu Ala Ala Gly Leu Leu Glu Glu Leu
 245 250 255
 Arg Asp Phe His Arg Arg Tyr Asn Gln Lys Asn Val Ser Glu Asn Ser
 260 265 270
 Gln Asp Tyr Gln His Gly Ile Phe Gln Ser Ile Gly Phe Lys Glu Phe
 275 280 285
 His Glu Tyr Leu Ile Thr Glu Gly Lys Cys Thr Leu Glu Thr Ser Asn
 290 295 300
 Gln Leu Leu Lys Lys Gly Ile Glu Ala Leu Lys Gln Val Thr Lys Arg
 305 310 315 320
 Tyr Ala Arg Lys Gln Asn Arg Trp Val Lys Asn Arg Phe Leu Ser Arg
 325 330 335
 Pro Gly Pro Ile Val Pro Pro Val Tyr Gly Leu Glu Val Ser Asp Val
 340 345 350
 Ser Lys Trp Glu Glu Ser Val Leu Glu Pro Ala Leu Glu Ile Val Gln
 355 360 365
 Ser Phe Ile Gln Gly His Lys Pro Thr Ala Thr Pro Ile Lys Met Pro
 370 375 380
 Tyr Asn Glu Ala Glu Asn Lys Arg Ser Tyr His Leu Cys Asp Leu Cys
 385 390 395 400
 Asp Arg Ile Ile Ile Gly Asp Arg Glu Trp Ala Ala His Ile Lys Ser
 405 410 415
 Lys Ser His Leu Asn Gln Leu Lys Lys Arg Arg Arg Leu Asp Ser Asp
 420 425 430
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 Glu Pro Lys Glu Lys Gly Ser Pro Gly Gln Asn Asp Gln Glu Leu Lys
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 Cys Ser Val
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<210> 154
 <211> 4495
 <212> DNA
 <213> Homo sapiens

<400> 154

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<211> 1066

<212> PRT

<213> Homo sapiens

<400> 155

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Gln Gln Arg Tyr Leu Leu Leu Ala Gly Ala Pro Arg Glu Leu Ala Val
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Pro Asp Gly Tyr Thr Asn Arg Thr Gly Ala Val Tyr Leu Cys Pro Leu
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Thr Ala His Lys Asp Asp Cys Glu Arg Met Asn Ile Thr Val Lys Asn
100          105          110
Asp Pro Gly His His Ile Ile Glu Asp Met Trp Leu Gly Val Thr Val
115          120          125
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Thr Gln Val Leu Trp Ser Gly Ser Glu Asp Gln Arg Arg Met Val Gly
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Lys Cys Tyr Val Arg Gly Asn Asp Leu Glu Leu Asp Ser Ser Asp Asp
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Gln	Asp	Ile	Ala	Val	Gly	Ala	Pro	Phe	Glu	Gly	Leu	Gly	Lys	Val	Tyr
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Thr	Leu	Ala	Tyr	Thr	Leu	Glu	Ala	Asp	Arg	Asp	Arg	Arg	Pro	Pro	Arg
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His Arg Leu Gln Ser Phe Phe Gly Gly Thr Val Met Gly Glu Ser Gly
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<211> 8747

<212> DNA

<213> Homo sapiens

<400> 156

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<211> 769

<212> PRT

<213> Homo sapiens

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Cys Gly Trp Cys Val Gln Glu Asp Phe Ile Ser Gly Gly Ser Arg Ser
65     70     75     80
Glu Arg Cys Asp Ile Val Ser Asn Leu Ile Ser Lys Gly Cys Ser Val
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Pro Gly Ala Glu Ala Asn Phe Met Leu Lys Val His Pro Leu Lys Lys
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<211> 624

<212> PRT

<213> Homo sapiens

<400> 159

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Ser Ala Ile Ile Gly Gly Ser His Ser Lys Asn Tyr Val Leu Trp Glu
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Tyr Gly Gly Tyr Ala Ser Glu Gly Val Lys Gln Val Ala Glu Leu Gly
 65           70           75           80
Ser Pro Val Lys Met Glu Glu Glu Ile Arg Gln Gln Ser Asp Glu Val
 85           90           95
Leu Thr Val Ile Lys Ala Lys Ala Gln Trp Pro Ala Trp Gln Pro Leu
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Asn Val Arg Ala Ala Pro Ser Ala Glu Phe Ser Val Asp Arg Thr Arg
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His Leu Met Ser Phe Leu Thr Met Met Gly Pro Ser Pro Asp Trp Asn

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Arg Lys Lys Cys Arg	Ile Arg Lys Cys Leu	Arg Asn Pro Ser Ile Gln
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Lys Glu Glu Ser Glu	Gly Glu Gln Phe Pro	Gly Cys Arg Met Arg Pro
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174

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<211> 421

<212> PRT

<213> Homo sapiens

<400> 165

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His Thr Val Gly Cys Asp Tyr Cys Gly Pro Leu Val Glu Ile Ala Arg
          35          40          45
Asn Arg Gly Cys Glu Ala Met Val Cys Asp Asn Leu Asn Leu Pro Phe
          50          55          60
Arg Asp Glu Gly Phe Asp Ala Ile Ile Ser Ile Gly Val Ile His His
65          70          75          80
Phe Ser Thr Lys Gln Arg Arg Ile Arg Ala Ile Lys Glu Met Ala Arg
          85          90          95
Val Leu Val Pro Gly Gly Gln Leu Met Ile Tyr Val Trp Ala Met Glu
          100          105          110
Gln Lys Asn Arg Arg Phe Glu Lys Gln Asp Val Leu Val Pro Trp Asn
          115          120          125
Arg Ala Leu Cys Ser Gln Leu Phe Ser Glu Ser Ser Gln Ser Gly Arg
          130          135          140
Lys Arg Gln Cys Gly Tyr Pro Glu Arg Gly His Pro Tyr His Pro Pro
145          150          155          160
Cys Ser Glu Cys Ser Cys Ser Val Cys Phe Lys Glu Gln Gly Gly Ser
          165          170          175
Lys Arg Ser His Ser Val Gly Tyr Glu Pro Ala Met Ala Arg Thr Cys
          180          185          190
Phe Ala Asn Ile Ser Lys Glu Gly Glu Glu Glu Tyr Gly Phe Tyr Ser
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Thr Leu Gly Lys Ser Phe Arg Ser Trp Phe Phe Ser Arg Ser Leu Asp
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 Ser Ser Leu Asp Phe Asp His Gln Glu Pro Phe Ser Thr Lys Glu Gln
 260 265 270
 Ser Leu Asp Glu Glu Val Phe Val Glu Ser Ser Ser Gly Lys His Leu
 275 280 285
 Glu Trp Leu Arg Ala Pro Gly Thr Leu Lys His Leu Asn Gly Asp His
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 Gln Gly Glu Met Arg Arg Asn Gly Gly Gly Asn Phe Leu Asp Ser Thr
 305 310 315 320
 Asn Thr Gly Val Asn Cys Val Asp Ala Gly Asn Ile Glu Asp Asp Asn
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 Pro Ser Ala Ser Lys Ile Leu Arg Arg Ile Ser Ala Val Asp Ser Thr
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 Asp Phe Asn Pro Asp Asp Thr Met Ser Val Glu Asp Pro Gln Thr Asp
 355 360 365
 Val Leu Asp Ser Thr Ala Phe Met Arg Tyr Tyr His Val Phe Arg Glu
 370 375 380
 Gly Glu Leu Cys Ser Leu Leu Lys Glu Asn Val Ser Glu Leu Arg Ile
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<210> 166

<211> 1454

<212> DNA

<213> Homo sapiens

<400> 166

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180

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 <211> 276
 <212> PRT
 <213> Homo sapiens

<400> 167
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 35 40 45
 Gly Ala Pro Cys Ala Arg Gly Ser Gln Pro Trp Gln Val Ser Leu Phe
 50 55 60
 Asn Gly Leu Ser Phe His Cys Ala Gly Val Leu Val Asp Gln Ser Trp
 65 70 75 80
 Val Leu Thr Ala Ala His Cys Gly Asn Lys Pro Leu Trp Ala Arg Val
 85 90 95
 Gly Asp Asp His Leu Leu Leu Leu Gln Gly Glu Gln Leu Arg Arg Thr
 100 105 110
 Thr Arg Ser Val Val His Pro Lys Tyr His Gln Gly Ser Gly Pro Ile
 115 120 125
 Leu Pro Arg Arg Thr Asp Glu His Asp Leu Met Leu Leu Lys Leu Ala
 130 135 140
 Arg Pro Val Val Pro Gly Pro Arg Val Arg Ala Leu Gln Leu Pro Tyr
 145 150 155 160
 Arg Cys Ala Gln Pro Gly Asp Gln Cys Gln Val Ala Gly Trp Gly Thr
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 Thr Ala Ala Arg Arg Val Lys Tyr Asn Lys Gly Leu Thr Cys Ser Ser
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 Ile Thr Ile Leu Ser Pro Lys Glu Cys Glu Val Phe Tyr Pro Gly Val
 195 200 205
 Val Thr Asn Asn Met Ile Cys Ala Gly Leu Asp Arg Gly Gln Asp Pro
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 Cys Gln Ser Asp Ser Gly Gly Pro Leu Val Cys Asp Glu Thr Leu Gln
 225 230 235 240
 Gly Ile Leu Ser Trp Gly Val Tyr Pro Cys Gly Ser Ala Gln His Pro
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 Ala Val Tyr Thr Gln Ile Cys Lys Tyr Met Ser Trp Ile Asn Lys Val
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 <211> 1506
 <212> DNA
 <213> Homo sapiens

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<210> 169

<211> 244

<212> PRT

<213> Homo sapiens

<400> 169

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His Pro Tyr Gln Ala Ala Leu Tyr Thr Ser Gly His Leu Leu Cys Gly
          35          40          45
Gly Val Leu Ile His Pro Leu Trp Val Leu Thr Ala Ala His Cys Lys
          50          55          60
Lys Pro Asn Leu Gln Val Phe Leu Gly Lys His Asn Leu Arg Gln Arg
          65          70          75          80
Glu Ser Ser Gln Glu Gln Ser Ser Val Val Arg Ala Val Ile His Pro
          85          90          95
Asp Tyr Asp Ala Ala Ser His Asp Gln Asp Ile Met Leu Leu Arg Leu
          100          105          110
Ala Arg Pro Ala Lys Leu Ser Glu Leu Ile Gln Pro Leu Pro Leu Glu
          115          120          125
Arg Asp Cys Ser Ala Asn Thr Thr Ser Cys His Ile Leu Gly Trp Gly
          130          135          140
Lys Thr Ala Asp Gly Asp Phe Pro Asp Thr Ile Gln Cys Ala Tyr Ile
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His Leu Val Ser Arg Glu Glu Cys Glu His Ala Tyr Pro Gly Gln Ile
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Thr Gln Asn Met Leu Cys Ala Gly Asp Glu Lys Tyr Gly Lys Asp Ser
          180          185          190
Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Gly Asp His Leu Arg
          195          200          205
Gly Leu Val Ser Trp Gly Asn Ile Pro Cys Gly Ser Lys Glu Lys Pro
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230

235

240

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<212> DNA
<213> Homo sapiens

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cacaatcaca agaagattcc caccctgcc tccatgcct ggtcccaga cagtgaaca 1560
gctctggaag tgatgtcaga atagcttcca ataaagcagc ctcatcttga ggcctgagt 1620
atccaaaaaa aaaaaaaaaa a 1641

<210> 171
<211> 469
<212> PRT
<213> Homo sapiens

<400> 171
Met Ser Ile His Phe Ser Ser Pro Val Phe Thr Ser Arg Ser Ala Ala
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Phe Ser Gly Arg Gly Ala Gln Val Arg Leu Ser Ser Ala Arg Pro Gly
20 25 30
Gly Leu Gly Ser Ser Ser Leu Tyr Gly Leu Gly Ala Ser Arg Pro Arg
35 40 45
Val Ala Val Arg Ser Ala Tyr Gly Gly Pro Val Gly Ala Gly Ile Arg
50 55 60
Glu Val Thr Ile Asn Gln Ser Leu Leu Ala Pro Leu Arg Leu Asp Ala
65 70 75 80
Asp Pro Ser Leu Gln Arg Val Arg Gln Glu Glu Ser Glu Gln Ile Lys
85 90 95

183

Ala Leu Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu
 100 105 110
 Glu Gln Gln Asn Lys Leu Leu Glu Thr Lys Trp Thr Leu Leu Gln Glu
 115 120 125
 Gln Lys Ser Ala Lys Ser Ser Arg Leu Pro Asp Ile Phe Glu Ala Gln
 130 135 140
 Ile Ala Gly Leu Arg Gly Gln Leu Glu Ala Leu Gln Val Asp Gly Gly
 145 150 155 160
 Arg Leu Glu Gln Gly Leu Arg Thr Met Gln Asp Val Val Glu Asp Phe
 165 170 175
 Lys Asn Lys Tyr Glu Asp Glu Ile Asn Arg Arg Thr Ala Ala Glu Asn
 180 185 190
 Glu Phe Val Val Leu Lys Lys Asp Val Asp Ala Ala Tyr Met Ser Lys
 195 200 205
 Val Glu Leu Glu Ala Lys Val Asp Ala Leu Asn Asp Glu Ile Asn Phe
 210 215 220
 Leu Arg Thr Leu Asn Glu Thr Glu Leu Thr Glu Leu Gln Ser Gln Ile
 225 230 235 240
 Ser Asp Thr Ser Val Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp
 245 250 255
 Leu Asp Gly Ile Ile Ala Glu Val Lys Ala Gln Tyr Glu Glu Met Ala
 260 265 270
 Lys Cys Ser Arg Ala Glu Ala Glu Ala Trp Tyr Gln Thr Lys Phe Glu
 275 280 285
 Thr Leu Gln Ala Gln Ala Gly Lys His Gly Asp Asp Leu Arg Asn Thr
 290 295 300
 Arg Asn Glu Ile Ser Glu Met Asn Arg Ala Ile Gln Arg Leu Gln Ala
 305 310 315 320
 Glu Ile Asp Asn Ile Lys Asn Gln Arg Ala Lys Leu Glu Ala Ala Ile
 325 330 335
 Ala Glu Ala Glu Glu Cys Gly Glu Leu Ala Leu Lys Asp Ala Arg Ala
 340 345 350
 Lys Gln Glu Glu Leu Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met
 355 360 365
 Ala Arg Gln Leu Arg Glu Tyr Gln Glu Leu Met Ser Val Lys Leu Ala
 370 375 380
 Leu Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Glu Gly Glu Glu
 385 390 395 400
 Ser Arg Leu Ala Gly Asp Gly Val Gly Ala Val Asn Ile Ser Val Met
 405 410 415
 Asn Ser Thr Gly Gly Ser Ser Ser Gly Gly Gly Ile Gly Leu Thr Leu
 420 425 430
 Gly Gly Thr Met Gly Ser Asn Ala Leu Ser Phe Ser Ser Ser Ala Gly
 435 440 445
 Pro Gly Leu Leu Lys Ala Tyr Ser Ile Arg Thr Ala Ser Ala Ser Arg
 450 455 460
 Arg Ser Ala Arg Asp
 465

<210> 172

<211> 1640

<212> DNA

<213> Homo sapiens

<400> 172

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agggtgcgcct gagctccgct cgccccggcg gccttggcag cagcagcctc tacggcctcg 180
gcgcctcgcg gccgcgcgtg gccgtgcgct ctgcctatgg gggcccggtg ggccgcggca 240
tccgcgaggt caccattaac cagagcctgc tggccccgct gcggtggac gccgaccct 300
ccctccagcg ggtgcgccag gaggagagcg agcagatcaa gaccctcaac aacaagtttg 360
cctccttcat cgacaaggtg cggtttcttg agcagcagaa caagctgctg gagaccaagt 420
ggacgctgct gcaggagcag aagtcggcca agagcagccg cctcccagac atctttgagg 480
cccagattgc tggccttcgg ggtcagcttg aggcactgca ggtggatggg ggccgccttg 540
aggcgaggct gcggagcatg caggatgtgg tggaggactt caagaataag tacgaagatg 600
aaattaaccg ccgcacagct gctgagaatg agtttgtggt gctgaagaag gatgtggatg 660
ctgcctacat gagcaaggtg gagctggagg ccaaggtgga tgccctgaat gatgagatca 720
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catctgtggt gctgtccatg gacaacagtc gctccctgga cctggacggc atcatcgctg 840
aggtaaggc acagtatgag gagatggcca aatgcagccg ggctgaggct gaagcctggt 900
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acaatcacia gaagattccc acccctgcct cccatgcctg gtccaagac agtgagacag 1560
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<210> 173

<211> 469

<212> PRT

<213> Homo sapiens

<400> 173

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Met Ser Ile His Phe Ser Ser Pro Val Phe Thr Ser Arg Ser Ala Ala
1      5      10      15
Phe Ser Gly Arg Gly Ala Gln Val Arg Leu Ser Ser Ala Arg Pro Gly
20      25      30
Gly Leu Gly Ser Ser Ser Leu Tyr Gly Leu Gly Ala Ser Arg Pro Arg
35      40      45
Val Ala Val Arg Ser Ala Tyr Gly Gly Pro Val Gly Ala Gly Ile Arg
50      55      60
Glu Val Thr Ile Asn Gln Ser Leu Leu Ala Pro Leu Arg Leu Asp Ala
65      70      75      80
Asp Pro Ser Leu Gln Arg Val Arg Gln Glu Glu Ser Glu Gln Ile Lys
85      90      95
Thr Leu Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu
100     105     110
Glu Gln Gln Asn Lys Leu Leu Glu Thr Lys Trp Thr Leu Leu Gln Glu
115     120     125
Gln Lys Ser Ala Lys Ser Ser Arg Leu Pro Asp Ile Phe Glu Ala Gln
130     135     140
Ile Ala Gly Leu Arg Gly Gln Leu Glu Ala Leu Gln Val Asp Gly Gly
145     150     155     160
Arg Leu Glu Ala Glu Leu Arg Ser Met Gln Asp Val Val Glu Asp Phe
165     170     175
Lys Asn Lys Tyr Glu Asp Glu Ile Asn Arg Arg Thr Ala Ala Glu Asn
180     185     190
Glu Phe Val Val Leu Lys Lys Asp Val Asp Ala Ala Tyr Met Ser Lys

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185

Val	Glu	Leu	Glu	Ala	Lys	Val	Asp	Ala	Leu	Asn	Asp	Glu	Ile	Asn	Phe
210						215					220				
Leu	Arg	Thr	Leu	Asn	Glu	Thr	Glu	Leu	Thr	Glu	Leu	Gln	Ser	Gln	Ile
225				230						235					240
Ser	Asp	Thr	Ser	Val	Val	Leu	Ser	Met	Asp	Asn	Ser	Arg	Ser	Leu	Asp
				245					250					255	
Leu	Asp	Gly	Ile	Ile	Ala	Glu	Val	Lys	Ala	Gln	Tyr	Glu	Glu	Met	Ala
			260					265					270		
Lys	Cys	Ser	Arg	Ala	Glu	Ala	Glu	Ala	Trp	Tyr	Gln	Thr	Lys	Phe	Glu
	275						280					285			
Thr	Leu	Gln	Ala	Gln	Ala	Gly	Lys	His	Gly	Asp	Asp	Leu	Arg	Asn	Thr
290						295					300				
Arg	Asn	Glu	Ile	Ser	Glu	Met	Asn	Arg	Ala	Ile	Gln	Arg	Leu	Gln	Ala
305					310					315					320
Glu	Ile	Asp	Asn	Ile	Lys	Asn	Gln	Arg	Ala	Lys	Leu	Glu	Ala	Ala	Ile
			325						330					335	
Ala	Glu	Ala	Glu	Glu	Arg	Gly	Glu	Leu	Ala	Leu	Lys	Asp	Ala	Arg	Ala
			340					345				350			
Lys	Gln	Glu	Glu	Leu	Glu	Ala	Ala	Leu	Gln	Arg	Ala	Lys	Gln	Asp	Met
	355						360					365			
Ala	Arg	Gln	Leu	Arg	Glu	Tyr	Gln	Glu	Leu	Met	Ser	Val	Lys	Leu	Ala
370						375					380				
Leu	Asp	Ile	Glu	Ile	Ala	Thr	Tyr	Arg	Lys	Leu	Leu	Glu	Gly	Glu	Glu
385					390					395					400
Ser	Arg	Leu	Ala	Gly	Asp	Gly	Val	Gly	Ala	Val	Asn	Ile	Ser	Val	Met
			405					410						415	
Asn	Ser	Thr	Gly	Gly	Ser	Ser	Ser	Gly	Gly	Gly	Ile	Gly	Leu	Thr	Leu
		420						425					430		
Gly	Gly	Thr	Met	Gly	Ser	Asn	Ala	Leu	Ser	Phe	Ser	Ser	Ser	Ala	Gly
	435						440				445				
Pro	Gly	Leu	Leu	Lys	Ala	Tyr	Ser	Ile	Arg	Thr	Ala	Ser	Ala	Ser	Arg
450						455					460				
Arg	Ser	Ala	Arg	Asp											
465															

<210> 174

<211> 2186

<212> DNA

<213> Homo sapiens

<400> 174

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gtccgccgag ggcgacccac cggcccgtct cgcccgccgc gccggggagg tggagcacga 180
gcgcacgtgt taggacccca aagatggtga actatgacctg ggcagggcga agccagagga 240
aactctggtg gaggtccgta gcggtcctga cgtgcaaatc ggtcgtcoga cctgggtata 300
ggggcgggct ccaggcgagg cggtcgacgc tcctgaaaac ttgcgcgcgc gctcgcgcca 360
ctgcgcccgg agcgtgaag atggtcgcgc cctggacgcg gttctactcc aacagctgct 420
gcttgtgctg ccatgtccgc accggcacca tcctgctcgg cgtctggtat ctgatcatca 480
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caagttctga actgggaggt gactttgagt tcatggatga tgccaacatg tgcattgcca 600
ttgcgatttc tcttctcatg atcctgatat gtgctatggc tacttacgga gcgtacaagc 660
aacgcgcagc ctggatcatc ccattcttct gttaccagat ctttgacttt gccctgaaca 720
tggttggtgc aatcaactgtg cttatttata caaactccat tcaggaatac atacggcaac 780
tgccctcctaa ttttccctac agagatgatg tcatgtcagt gaatcctacc tgtttggtcc 840
ttattattct tctgtttatt agcattatct tgacttttaa gggttacttg attagctggt 900

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ccaaggagcc accgccacct tacgtgtctg cctaagcctt caagtgggcg gagctgaggg 1080
cagcagcttg actttgcaga catctgagca atagtctgtg tatttcactt ttgccatgag 1140
cctctctgag cttgtttgtt gctgaaatgc tactttttta aatttagatg ttagattgaa 1200
aactgtagtt ttcaacatat gctttgctag aacactgtga tagattaact gtagaattct 1260
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ctagtccact tttaaaatgt aaacattttc agaaaaatga ggattgcctt ccttgtatgc 2040
gctttttacc ttgactacct gaattgcaag ggatttttat atattcatat gttacaaagt 2100
cagcaactct cctgttggtt cattattgaa tgtgctgtaa attaagttgt ttgcaattaa 2160
aacaaggttt gcccaaaaa aaaaaa 2186

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<210> 175

<211> 283

<212> PRT

<213> Homo sapiens

<400> 175

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Met Val Asn Tyr Ala Trp Ala Gly Arg Ser Gln Arg Lys Leu Trp Trp
 1           5           10           15
Arg Ser Val Ala Val Leu Thr Cys Lys Ser Val Val Arg Pro Gly Tyr
          20          25          30
Arg Gly Gly Leu Gln Ala Arg Arg Ser Thr Leu Leu Lys Thr Cys Ala
          35          40          45
Arg Ala Arg Ala Thr Ala Pro Gly Ala Met Lys Met Val Ala Pro Trp
          50          55          60
Thr Arg Phe Tyr Ser Asn Ser Cys Cys Leu Cys Cys His Val Arg Thr
          65          70          75          80
Gly Thr Ile Leu Leu Gly Val Trp Tyr Leu Ile Ile Asn Ala Val Val
          85          90          95
Leu Leu Ile Leu Leu Ser Ala Leu Ala Asp Pro Asp Gln Tyr Asn Phe
          100          105          110
Ser Ser Ser Glu Leu Gly Gly Asp Phe Glu Phe Met Asp Asp Ala Asn
          115          120          125
Met Cys Ile Ala Ile Ala Ile Ser Leu Leu Met Ile Leu Ile Cys Ala
          130          135          140
Met Ala Thr Tyr Gly Ala Tyr Lys Gln Arg Ala Ala Trp Ile Ile Pro
          145          150          155          160
Phe Phe Cys Tyr Gln Ile Phe Asp Phe Ala Leu Asn Met Leu Val Ala
          165          170          175
Ile Thr Val Leu Ile Tyr Pro Asn Ser Ile Gln Glu Tyr Ile Arg Gln
          180          185          190
Leu Pro Pro Asn Phe Pro Tyr Arg Asp Asp Val Met Ser Val Asn Pro
          195          200          205
Thr Cys Leu Val Leu Ile Ile Leu Leu Phe Ile Ser Ile Ile Leu Thr
          210          215          220
Phe Lys Gly Tyr Leu Ile Ser Cys Val Trp Asn Cys Tyr Arg Tyr Ile

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187

225		230		235		240
Asn Gly Arg Asn Ser	Ser Asp Val Leu Val Tyr Val Thr Ser Asn Asp					
	245		250			255
Thr Thr Val Leu Leu Pro Pro Tyr Asp Asp Ala Thr Val Asn Gly Ala						
	260		265			270
Ala Lys Glu Pro Pro Pro Pro Tyr Val Ser Ala						
	275		280			

<210> 176
 <211> 597
 <212> DNA
 <213> Homo sapiens

<400> 176
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 aacttccagg acaaccaatt ccagggggaag tggatatgtgg taggcctggc aggggaatgca 180
 attctcagag aagacaaaaga ccgcgcaaaag atgtatgcca ccatctatga gctgaaagaa 240
 gacaagagct acaatgtcac ctccgtcctg tttaggaaaa agaagtgtga ctactggatc 300
 aggacttttg ttccagggtg ccagcccggc gagttcacgc tgggcaacat taagagttac 360
 cctggattaa cgagttacct cgtccgagtg gtgagcacca actacaacca gcatgctatg 420
 gtgttcttca agaaagtttc tcaaaacagg gactacttca agatcaccct ctacggggaga 480
 accaaggagc tgacttcgga actaaaggag aacttcatcc gcttctccaa atatctgggc 540
 ctccctgaaa accacatcgt cttccctgtc ccaatcgacc agtgtatcga cggtga 597

<210> 177
 <211> 198
 <212> PRT
 <213> Homo sapiens

<400> 177
 Met Pro Leu Gly Leu Leu Trp Leu Gly Leu Ala Leu Leu Gly Ala Leu
 1 5 10 15
 His Ala Gln Ala Gln Asp Ser Thr Ser Asp Leu Ile Pro Ala Pro Pro
 20 25 30
 Leu Ser Lys Val Pro Leu Gln Gln Asn Phe Gln Asp Asn Gln Phe Gln
 35 40 45
 Gly Lys Trp Tyr Val Val Gly Leu Ala Gly Asn Ala Ile Leu Arg Glu
 50 55 60
 Asp Lys Asp Pro Gln Lys Met Tyr Ala Thr Ile Tyr Glu Leu Lys Glu
 65 70 75 80
 Asp Lys Ser Tyr Asn Val Thr Ser Val Leu Phe Arg Lys Lys Lys Cys
 85 90 95
 Asp Tyr Trp Ile Arg Thr Phe Val Pro Gly Cys Gln Pro Gly Glu Phe
 100 105 110
 Thr Leu Gly Asn Ile Lys Ser Tyr Pro Gly Leu Thr Ser Tyr Leu Val
 115 120 125
 Arg Val Val Ser Thr Asn Tyr Asn Gln His Ala Met Val Phe Phe Lys
 130 135 140
 Lys Val Ser Gln Asn Arg Glu Tyr Phe Lys Ile Thr Leu Tyr Gly Arg
 145 150 155 160
 Thr Lys Glu Leu Thr Ser Glu Leu Lys Glu Asn Phe Ile Arg Phe Ser
 165 170 175
 Lys Tyr Leu Gly Leu Pro Glu Asn His Ile Val Phe Pro Val Pro Ile
 180 185 190
 Asp Gln Cys Ile Asp Gly
 195

<210> 178
 <211> 1518
 <212> DNA
 <213> Homo sapiens

<400> 178
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 gggcagcacc atgcagcccc tgtggctctg ctgggcactc tgggtgttgc cctgggccag 120
 ccccggggcc gccctgaccg gggagcagct cctgggcagc ctgctgcggc agctgcagct 180
 caaagagggtg cccaccctgg acagggccga catggaggag ctggatcatc ccaccacgt 240
 gagggcccag tacgtggccc tgctgcagcg cagccacggg gaccgctccc gcggaaagag 300
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 gctgcggctc ttccaggagc cgggtcccaa ggccgcgctg cacaggcacg ggccgctgtc 480
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 gctgggtccgc tttgcctcgc agggggcgcc agccgggctt ggggagcccc agctggagct 780
 gcacaccctg gaccttgggg actatggagc tcagggcgac tgtgaccctg aagcaccaat 840
 gaccgagggc acccgctgct gccgccagga gatgtacatt gacctgcagg ggatgaagtg 900
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 cgccctcggag actgactcgc tgcccatgat cgtcagcatc aaggaggagg gcaggaccag 1080
 gccccagggtg gtcagcctgc ccaacatgag ggtgcagaag tgcagctgtg cctcggatgg 1140
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 gttttctcta ttcttattat tcaactgcact atattctaag cacttacatg tggagatact 1440
 gtaacctgag ggcagaaagc ccaatgtgtc attgtttact tgtcctgtca ctggatctgg 1500
 gctaaagtcc tccaccac 1518

<210> 179
 <211> 366
 <212> PRT
 <213> Homo sapiens

<400> 179
 Met Gln Pro Leu Trp Leu Cys Trp Ala Leu Trp Val Leu Pro Leu Ala
 1 5 10 15
 Ser Pro Gly Ala Leu Thr Gly Glu Gln Leu Leu Gly Ser Leu Leu
 20 25 30
 Arg Gln Leu Gln Leu Lys Glu Val Pro Thr Leu Asp Arg Ala Asp Met
 35 40 45
 Glu Glu Leu Val Ile Pro Thr His Val Arg Ala Gln Tyr Val Ala Leu
 50 55 60
 Leu Gln Arg Ser His Gly Asp Arg Ser Arg Gly Lys Arg Phe Ser Gln
 65 70 75 80
 Ser Phe Arg Glu Val Ala Gly Arg Phe Leu Ala Leu Glu Ala Ser Thr
 85 90 95
 His Leu Leu Val Phe Gly Met Glu Gln Arg Leu Pro Pro Asn Ser Glu
 100 105 110
 Leu Val Gln Ala Val Leu Arg Leu Phe Gln Glu Pro Val Pro Lys Ala
 115 120 125
 Ala Leu His Arg His Gly Arg Leu Ser Pro Arg Ser Ala Arg Ala Arg

189

130	135	140
Val Thr Val Glu Trp	Leu Arg Val Arg Asp Asp	Gly Ser Asn Arg Thr
145	150	155
Ser Leu Ile Asp Ser	Arg Leu Val Ser Val His	Glu Ser Gly Trp Lys
	165	170
Ala Phe Asp Val Thr	Glu Ala Val Asn Phe Trp	Gln Gln Leu Ser Arg
	180	185
Pro Arg Gln Pro Leu	Leu Leu Gln Val Ser Val	Gln Arg Glu His Leu
	195	200
Gly Pro Leu Ala Ser	Gly Ala His Lys Leu Val	Arg Phe Ala Ser Gln
	210	215
Gly Ala Pro Ala Gly	Leu Gly Glu Pro Gln Leu	Glu Leu His Thr Leu
225	230	235
Asp Leu Gly Asp Tyr	Gly Ala Gln Gly Asp Cys	Asp Pro Glu Ala Pro
	245	250
Met Thr Glu Gly Thr	Arg Cys Cys Arg Gln Glu	Met Tyr Ile Asp Leu
	260	265
Gln Gly Met Lys Trp	Ala Glu Asn Trp Val Leu	Glu Pro Pro Gly Phe
	275	280
Leu Ala Tyr Glu Cys	Val Gly Thr Cys Arg Gln	Pro Pro Glu Ala Leu
	290	295
Ala Phe Lys Trp Pro	Phe Leu Gly Pro Arg Gln	Cys Ile Ala Ser Glu
305	310	315
Thr Asp Ser Leu Pro	Met Ile Val Ser Ile Lys	Glu Gly Gly Arg Thr
	325	330
Arg Pro Gln Val Val	Ser Leu Pro Asn Met Arg	Val Gln Lys Cys Ser
	340	345
Cys Ala Ser Asp Gly	Ala Leu Val Pro Arg Arg	Leu Gln Pro
	355	360

<210> 180
 <211> 444
 <212> DNA
 <213> Homo sapiens

<400> 180
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 aatgccgagt tctgcccagc tcttggtttct gagctgttag acttcttctt cattagtgaa 180
 cctctgttca agttaagtct tgccaaatct gatgccctc cggaagctgt tgcagccaag 240
 ttaggagtga agagatgcac ggatcagatg tcccttcaga aacgaagcct cattgcggaa 300
 gtcctgtgta aaatattgaa gaaatgtagt gtgtgacatg taaaaacttt catcctgggt 360
 tccactgtct ttcaatgaca ccctgatctt cactgcagaa tgtaaagggt tcaacgtctt 420
 gctttaataa atcacttgct ctac 444

<210> 181
 <211> 90
 <212> PRT
 <213> Homo sapiens

<400> 181
 Met Lys Leu Ser Val Cys Leu Leu Leu Val Thr Leu Ala Leu Cys Cys
 1 5 10 15
 Tyr Gln Ala Asn Ala Glu Phe Cys Pro Ala Leu Val Ser Glu Leu Leu
 20 25 30
 Asp Phe Phe Phe Ile Ser Glu Pro Leu Phe Lys Leu Ser Leu Ala Lys
 35 40 45

190

Phe Asp Ala Pro Pro Glu Ala Val Ala Ala Lys Leu Gly Val Lys Arg
 50 55 60
 Cys Thr Asp Gln Met Ser Leu Gln Lys Arg Ser Leu Ile Ala Glu Val
 65 70 75 80
 Leu Val Lys Ile Leu Lys Lys Cys Ser Val
 85 90

<210> 182
 <211> 754
 <212> DNA
 <213> Homo sapiens

<400> 182
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 gtccaagctg caagatgacc tcaaggaggc aatgaatact atgatgtgta gccgatgccca 120
 aggaaagcat aggaggtttg aaatggaccg ggaacctaag agtgccagat actgtgctga 180
 gtgtaatagg ctgcatcctg ctgaggaagg agacttttgg gcagagtcaa gcatgttggg 240
 cctcaagatc acctactttg cactgatgga tggaaagggtg tatgacatca cagagtgggc 300
 tggatgccag cgtgtaggta tctccccaga taccacaga gtccccctatc acatctcatt 360
 tggttctcgg attccaggca ccagaggcg gcagagagcc accccagatg cccctcctgc 420
 tgatcttcag gatttcttga gtcggatott tcaagtaccc ccagggcaga tgccaatggg 480
 aacttctttg cagctcctca gcctgcccct ggagccgctg cagcctctaa gcccaacagc 540
 acagtaccca agggagaagc caaacctaag cggcggaaga aagtgaggag gcccttccaa 600
 cggttgatgcc ctttctcttt cctcaaatca atgtcaggga gtcaaaaggg ctgtagcaca 660
 ggatggagtt tgatttatcc ctctccccc aacacctagg aactgaatct ttttcttttt 720
 attttttgag atggagtctt gctctgttgc ccag 754

<210> 183
 <211> 191
 <212> PRT
 <213> Homo sapiens

<400> 183
 Met Lys Arg Met Ala Glu Asn Glu Leu Ser Arg Ser Val Asn Glu Phe
 1 5 10 15
 Leu Ser Lys Leu Gln Asp Asp Leu Lys Glu Ala Met Asn Thr Met Met
 20 25 30
 Cys Ser Arg Cys Gln Gly Lys His Arg Arg Phe Glu Met Asp Arg Glu
 35 40 45
 Pro Lys Ser Ala Arg Tyr Cys Ala Glu Cys Asn Arg Leu His Pro Ala
 50 55 60
 Glu Glu Gly Asp Phe Trp Ala Glu Ser Ser Met Leu Gly Leu Lys Ile
 65 70 75 80
 Thr Tyr Phe Ala Leu Met Asp Gly Lys Val Tyr Asp Ile Thr Glu Trp
 85 90 95
 Ala Gly Cys Gln Arg Val Gly Ile Ser Pro Asp Thr His Arg Val Pro
 100 105 110
 Tyr His Ile Ser Phe Gly Ser Arg Ile Pro Gly Thr Arg Gly Arg Gln
 115 120 125
 Arg Ala Thr Pro Asp Ala Pro Pro Ala Asp Leu Gln Asp Phe Leu Ser
 130 135 140
 Arg Ile Phe Gln Val Pro Pro Gly Gln Met Pro Met Gly Thr Ser Leu
 145 150 155 160
 Gln Leu Leu Ser Leu Pro Leu Glu Pro Leu Gln Pro Leu Ser Pro Thr
 165 170 175
 Ala Gln Tyr Pro Arg Glu Lys Pro Asn Leu Ser Gly Gly Arg Lys
 180 185 190

<210> 184
 <211> 2511
 <212> DNA
 <213> Homo sapiens

<400> 184
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 tcccctccac gatgtatggg gacccgcatg cagccaggtc catgcagccg gtccaccacc 180
 tgaaccacgg gcctcctctg cactcgcacg agtaccgca cacagctcat accaacgcca 240
 tggcccccag catgggctcc tctgtcaatg acgctttaa gagagataaa gatgccattt 300
 atggacaccc cctcttccct ctcttagcac tgatttttga gaaatgtgaa ttagctactt 360
 gtaccccccg cgagccgggg gtggcgggcg gggacgtctg ctgctcagag tcattcaatg 420
 aagatatagc cgtgtttgcc aaacagattc gcgcagaaaa acctctattt tcttctaata 480
 cagaactgga taacttgatg attcaagcca tacaagtatt aagggttcat ctattggaat 540
 tagagaaggt acacgaatta tgtgacaatt tctgccaccg gtatattagc tgtttgaaag 600
 ggaaaaatgcc tatcgatttg gtgatagacg atagagaagg aggatcaaaa tcagacagtg 660
 aagatataac aagatcagca aatctaactg accagcctc ttggaacaga gatcatgatg 720
 acacggcatc tactcgttca ggaggaaccc caggcccttc cagcggtgga cacacgtcac 780
 acagtgggga caacagcagt gagcaagggt atggcttga caacagtgtg gcttccccc 840
 gcacaggtga cgatgatgac cctgataagg acaaaaagcg tcacaaaaag cgtggcatct 900
 ttcccaaagt agccacaaat atcatgaggg cgtggctgtt ccagcatcta acacaccctt 960
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 tgaacaattg gtttattaat gcccgagaa gaatagtga gcccatgata gaccagtcga 1080
 accgagcagt aagtcaagga acaccttata atcctgatgg acagcccatg ggaggtttcg 1140
 taatggacgg tcagcaacat atgggaatta gagcaccagg acctatgagt ggaatgggca 1200
 tgaatatggg catggagggg cagtggcact acatgtaacc ttcacttagt taaccaatcg 1260
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 agggaccttt aaaaagcagg aaataccaac tgaagtcaat ttgggggaca tgctaaataa 1740
 ctatataaga cattaagaga acaaagagtg aatatgtga aatgctatta tactgttatc 1800
 catattacgt tgtttcttat agatttttta aaaaaaatgt gaaatttttc cacactatgt 1860
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 atcaggcaga agaatctttc ttctcgccta ggatttcagc catgcgcgcg ctctctctct 2040
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 tcattgtccc catgcaacaa ccaccacctt atacatcact tctgtttta agcagctcta 2340
 aaacatagac tgaagattta tttttaatat gttgacttta tttctgagca aagcatcggt 2400
 catgtgtgta ttttttcata gtcccacctt ggagcattta tgtagacatt gtaaataaat 2460
 tttgtgcaaa aaggactgga aaaatgaact gtattattgc aatttttttt t 2511

<210> 185
 <211> 390
 <212> PRT
 <213> Homo sapiens

<400> 185
 Met Ala Gln Arg Tyr Asp Asp Leu Pro His Tyr Gly Gly Met Asp Gly

192

1	5	10	15
Val Gly Ile Pro Ser Thr Met Tyr Gly Asp Pro His Ala Ala Arg Ser			
	20	25	30
Met Gln Pro Val His His Leu Asn His Gly Pro Pro Leu His Ser His			
	35	40	45
Gln Tyr Pro His Thr Ala His Thr Asn Ala Met Ala Pro Ser Met Gly			
	50	55	60
Ser Ser Val Asn Asp Ala Leu Lys Arg Asp Lys Asp Ala Ile Tyr Gly			
65	70	75	80
His Pro Leu Phe Pro Leu Leu Ala Leu Ile Phe Glu Lys Cys Glu Leu			
	85	90	95
Ala Thr Cys Thr Pro Arg Glu Pro Gly Val Ala Gly Gly Asp Val Cys			
	100	105	110
Ser Ser Glu Ser Phe Asn Glu Asp Ile Ala Val Phe Ala Lys Gln Ile			
	115	120	125
Arg Ala Glu Lys Pro Leu Phe Ser Ser Asn Pro Glu Leu Asp Asn Leu			
	130	135	140
Met Ile Gln Ala Ile Gln Val Leu Arg Phe His Leu Leu Glu Leu Glu			
145	150	155	160
Lys Val His Glu Leu Cys Asp Asn Phe Cys His Arg Tyr Ile Ser Cys			
	165	170	175
Leu Lys Gly Lys Met Pro Ile Asp Leu Val Ile Asp Asp Arg Glu Gly			
	180	185	190
Gly Ser Lys Ser Asp Ser Glu Asp Ile Thr Arg Ser Ala Asn Leu Thr			
	195	200	205
Asp Gln Pro Ser Trp Asn Arg Asp His Asp Asp Thr Ala Ser Thr Arg			
	210	215	220
Ser Gly Gly Thr Pro Gly Pro Ser Ser Gly Gly His Thr Ser His Ser			
225	230	235	240
Gly Asp Asn Ser Ser Glu Gln Gly Asp Gly Leu Asp Asn Ser Val Ala			
	245	250	255
Ser Pro Ser Thr Gly Asp Asp Asp Asp Pro Asp Lys Asp Lys Lys Arg			
	260	265	270
His Lys Lys Arg Gly Ile Phe Pro Lys Val Ala Thr Asn Ile Met Arg			
	275	280	285
Ala Trp Leu Phe Gln His Leu Thr His Pro Tyr Pro Ser Glu Glu Gln			
	290	295	300
Lys Lys Gln Leu Ala Gln Asp Thr Gly Leu Thr Ile Leu Gln Val Asn			
305	310	315	320
Asn Trp Phe Ile Asn Ala Arg Arg Arg Ile Val Gln Pro Met Ile Asp			
	325	330	335
Gln Ser Asn Arg Ala Val Ser Gln Gly Thr Pro Tyr Asn Pro Asp Gly			
	340	345	350
Gln Pro Met Gly Gly Phe Val Met Asp Gly Gln Gln His Met Gly Ile			
	355	360	365
Arg Ala Pro Gly Pro Met Ser Gly Met Gly Met Asn Met Gly Met Glu			
	370	375	380
Gly Gln Trp His Tyr Met			
385	390		

<210> 186

<211> 517

<212> DNA

<213> Homo sapiens

<400> 186

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193

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cgccatgaag ctgctgatgg tctcatgct ggccggccctc ctctgcact gctatgcaga 120
ttctggctgc aaactcctgg aggacatggg tgaagagacc atcaattccg acatatctat 180
acctgaatac aaagagcttc ttcaagagtt catagacagt gatgccgctg cagaggctat 240
ggggaaattc aagcagtgtt tctcaacca gtcacataga actctgaaa actttggact 300
gatgatgcat acagtgtacg acagcatttg gtgtaatatg aagagtaatt aactttaccc 360
aaggcgtttg gctcagaggg ctacagacta tggccagaac tcactgtttg attgctagaa 420
accacttttc tttcttgtgt tgtcttttta tgtggaaact gctagacaac tgttgaaacc 480
tcaaatcat ttccatttca ataactaact gcaaatc 517

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<210> 187

<211> 95

<212> PRT

<213> Homo sapiens

<400> 187

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Met Lys Leu Leu Met Val Leu Met Leu Ala Ala Leu Leu Leu His Cys
1          5          10          15
Tyr Ala Asp Ser Gly Cys Lys Leu Leu Glu Asp Met Val Glu Lys Thr
20          25          30
Ile Asn Ser Asp Ile Ser Ile Pro Glu Tyr Lys Glu Leu Leu Gln Glu
35          40          45
Phe Ile Asp Ser Asp Ala Ala Ala Glu Ala Met Gly Lys Phe Lys Gln
50          55          60
Cys Phe Leu Asn Gln Ser His Arg Thr Leu Lys Asn Phe Gly Leu Met
65          70          75          80
Met His Thr Val Tyr Asp Ser Ile Trp Cys Asn Met Lys Ser Asn
85          90          95

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<210> 188

<211> 2048

<212> DNA

<213> Homo sapiens

<400> 188

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ctgctgggca aaaatcagag ccgcctccgc cccattaccc atcatggaaa ccctccagga 120
aaaagtggcc ccggacgcgc gagcctgagg attctgcaca aaagagggtg ccaaaatgaa 180
gacctgatg gccatggtc tggcagtgtg tttagcgtc accaccatgt gcaccagctt 240
gttgctagtg tacagcagcc tcggcgccca gaaggagcgg ccccgccagc agcagcagca 300
gcagcagcaa cagcagcagc aggcgtccgc caccggcagc tcgcagccgg cggcggagag 360
cagcaccag cagcgcgccg gggctcccgc gggaccgcgg ccactggacg gatacctcgg 420
agtggcggac cacaagcccc tgaaaatgca ctgcagggac tgtgccctgg tgaccagctc 480
agggcatctg ctgcacagtc ggcaaggctc ccagattgac cagacagagt gtgtcatccg 540
catgaatgac gccccacac gcggtatagg gcgtgacgtg ggcaatcgca ccagcctgag 600
ggatcatcgc cattccagca tccagaggat cctccgcaac cgccatgacc tgctcaacgt 660
gagccagggc accgtgttca tcttctgggg cccagcagc tacatgcggc gggacggcaa 720
gggccaggtc tacaacaacc tgcatctcct gagccagggt ctgcccggc tgaaggcctt 780
catgattact cgccacaaga tgctgcagtt tgatgagctc ttcaagcagg agactggcaa 840
agacaggaag atatccaaca cttggctcag cactggctgg tttacaatga caattgact 900
ggagctctgt gacaggatca atgtttatgg catgggtgcc ccagacttct gcagggatcc 960
caatcaccct tcagtacctt atcattatta tgaacctttt ggacctgatg aatgtacaat 1020
gtacctctcc catgagcgag gacgcaaggg cagtcatcac cgctttatca cagagaaacg 1080
agtctttaag aactgggcac ggacattcaa tattcacttt tttcaaccag actggaaacc 1140
agaatcactt gctataaate atoctgagaa taaacctgtg ttctaaggaa tgagcatgcc 1200
agactgtaat ccagggtatt cactgcatca gacaccgaga cactgaactt cctgagccac 1260
cagacaggaa agggtagcag aaaacagctt cactcctcag gaagtacat ggacagacgc 1320
ctaccagggg tgacaaagca gtgcagttgg attgtaagga aaaattccgg aattaatgca 1380

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tcctaataagaa  tgggtgtcccc  ttcaatgggtg  ttaccttagg  agctgaacat  tcaattcagt  1440
tacaccacta  tgactaaaaa  cagtttggat  ctcttagtat  tgcctttgaa  actgcaacat  1500
aagcaactca  acaatattag  ttgcattcct  ttatagacat  accatgtcaa  agacgttttt  1560
ctatcaagtt  gtattctttc  ctgttctata  acctttgtca  tctgttagac  tctgtatgtg  1620
tgatttgtaa  aaagcaggct  gaaactatgg  acatgatttc  tgaagagcac  atctccactg  1680
actttcataa  agcaaagtgc  caatatttat  ttattgagag  ttttttagtg  caatctgggc  1740
cagtattttt  atagattatg  attatgtggt  aatttatcct  tcctaactct  ttaatcctga  1800
atgatgggtg  gaaatggcct  agaattaggt  tactctgttc  acaatgctca  ttgttagcat  1860
gcaattggta  tttgacttgg  aagtgttgtg  ttgtattttt  tgaaccctta  ggcttcagga  1920
aaactgctct  tttgtaaaaa  gaatagcgat  gacattttct  aatgtgcaga  aatgttccaa  1980
aaggacaaaa  ttgaaaacca  aaaactatgt  tattaaaaca  aaaaaatgct  aaaaaaaaaa  2040
aaaaaaaaa  2048

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<210> 189
 <211> 336
 <212> PRT
 <213> Homo sapiens

<400> 189

Met	Lys	Thr	Leu	Met	Arg	His	Gly	Leu	Ala	Val	Cys	Leu	Ala	Leu	Thr
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Thr	Met	Cys	Thr	Ser	Leu	Leu	Leu	Val	Tyr	Ser	Ser	Leu	Gly	Gly	Gln
			20					25					30		
Lys	Glu	Arg	Pro	Pro	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln	Gln
		35					40						45		
Gln	Ala	Ser	Ala	Thr	Gly	Ser	Ser	Gln	Pro	Ala	Ala	Glu	Ser	Ser	Thr
	50					55					60				
Gln	Gln	Arg	Pro	Gly	Val	Pro	Ala	Gly	Pro	Arg	Pro	Leu	Asp	Gly	Tyr
65					70					75					80
Leu	Gly	Val	Ala	Asp	His	Lys	Pro	Leu	Lys	Met	His	Cys	Arg	Asp	Cys
				85					90					95	
Ala	Leu	Val	Thr	Ser	Ser	Gly	His	Leu	Leu	His	Ser	Arg	Gln	Gly	Ser
			100					105					110		
Gln	Ile	Asp	Gln	Thr	Glu	Cys	Val	Ile	Arg	Met	Asn	Asp	Ala	Pro	Thr
	115						120					125			
Arg	Gly	Tyr	Gly	Arg	Asp	Val	Gly	Asn	Arg	Thr	Ser	Leu	Arg	Val	Ile
	130					135					140				
Ala	His	Ser	Ser	Ile	Gln	Arg	Ile	Leu	Arg	Asn	Arg	His	Asp	Leu	Leu
145					150				155						160
Asn	Val	Ser	Gln	Gly	Thr	Val	Phe	Ile	Phe	Trp	Gly	Pro	Ser	Ser	Tyr
			165					170						175	
Met	Arg	Arg	Asp	Gly	Lys	Gly	Gln	Val	Tyr	Asn	Asn	Leu	His	Leu	Leu
			180					185					190		
Ser	Gln	Val	Leu	Pro	Arg	Leu	Lys	Ala	Phe	Met	Ile	Thr	Arg	His	Lys
		195					200					205			
Met	Leu	Gln	Phe	Asp	Glu	Leu	Phe	Lys	Gln	Glu	Thr	Gly	Lys	Asp	Arg
	210					215					220				
Lys	Ile	Ser	Asn	Thr	Trp	Leu	Ser	Thr	Gly	Trp	Phe	Thr	Met	Thr	Ile
225					230					235					240
Ala	Leu	Glu	Leu	Cys	Asp	Arg	Ile	Asn	Val	Tyr	Gly	Met	Val	Pro	Pro
			245						250					255	
Asp	Phe	Cys	Arg	Asp	Pro	Asn	His	Pro	Ser	Val	Pro	Tyr	His	Tyr	Tyr
			260					265					270		
Glu	Pro	Phe	Gly	Pro	Asp	Glu	Cys	Thr	Met	Tyr	Leu	Ser	His	Glu	Arg
		275					280					285			
Gly	Arg	Lys	Gly	Ser	His	His	Arg	Phe	Ile	Thr	Glu	Lys	Arg	Val	Phe
	290					295					300				
Lys	Asn	Trp	Ala	Arg	Thr	Phe	Asn	Ile	His	Phe	Phe	Gln	Pro	Asp	Trp

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<210> 190
<211> 1078
<212> DNA
<213> Homo sapiens
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<210> 191
<211> 267
<212> PRT
<213> Homo sapiens
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<400> 191															
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1				5					10					15	
Ala	Leu	Pro	Leu	Pro	Gln	Glu	Ala	Gly	Gly	Met	Ser	Glu	Leu	Gln	Trp
			20					25					30		
Glu	Gln	Ala	Gln	Asp	Tyr	Leu	Lys	Arg	Phe	Tyr	Leu	Tyr	Asp	Ser	Glu
		35					40					45			
Thr	Lys	Asn	Ala	Asn	Ser	Leu	Glu	Ala	Lys	Leu	Lys	Glu	Met	Gln	Lys
	50					55					60				
Phe	Phe	Gly	Leu	Pro	Ile	Thr	Gly	Met	Leu	Asn	Ser	Arg	Val	Ile	Glu
65					70					75					80
Ile	Met	Gln	Lys	Pro	Arg	Cys	Gly	Val	Pro	Asp	Val	Ala	Glu	Tyr	Ser
				85					90					95	
Leu	Phe	Pro	Asn	Ser	Pro	Lys	Trp	Thr	Ser	Lys	Val	Val	Thr	Tyr	Arg
			100					105					110		
Ile	Val	Ser	Tyr	Thr	Arg	Asp	Leu	Pro	His	Ile	Thr	Val	Asp	Arg	Leu
		115					120					125			
Val	Ser	Lys	Ala	Leu	Asn	Met	Trp	Gly	Lys	Glu	Ile	Pro	Leu	His	Phe
	130					135					140				
Arg	Lys	Val	Val	Trp	Gly	Thr	Ala	Asp	Ile	Met	Ile	Gly	Phe	Ala	Arg
145					150					155					160
Gly	Ala	His	Gly	Asp	Ser	Tyr	Pro	Phe	Asp	Gly	Pro	Gly	Asn	Thr	Leu
				165					170					175	

196

Ala	His	Ala	Phe	Ala	Pro	Gly	Thr	Gly	Leu	Gly	Gly	Asp	Ala	His	Phe
		180						185					190		
Asp	Glu	Asp	Glu	Arg	Trp	Thr	Asp	Gly	Ser	Ser	Leu	Gly	Ile	Asn	Phe
		195					200					205			
Leu	Tyr	Ala	Ala	Thr	His	Glu	Leu	Gly	His	Ser	Leu	Gly	Met	Gly	His
		210				215					220				
Ser	Ser	Asp	Pro	Asn	Ala	Val	Met	Tyr	Pro	Thr	Tyr	Gly	Asn	Gly	Asp
225					230					235				240	
Pro	Gln	Asn	Phe	Lys	Leu	Ser	Gln	Asp	Asp	Ile	Lys	Gly	Ile	Gln	Lys
			245					250						255	
Leu	Tyr	Gly	Lys	Arg	Ser	Asn	Ser	Arg	Lys	Lys					
		260						265							

<210> 192

<211> 2217

<212> DNA

<213> Homo sapiens

<400> 192

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cctccctccc	tgggatctac	acagaccatg	gccttgccaa	cggctcgacc	cctggtgggg	120
tctgtggga	cccccgccct	cggcagcctc	ctgttcctgc	tcttcagcct	cggatgggtg	180
cagccctcga	ggaccctggc	tggagagaca	gggcaggagg	ctgcaccctt	ggacggagtc	240
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gcggaggtgt	ccggcctgag	cacggagcgt	gtccggggagc	tggctgtggc	cttggcacag	360
aagaatgtca	agctctcaac	agagcagctg	cgctgtcttg	ctcaccggct	ctctgagccc	420
cccgaggacc	tggacgcctt	cccattggac	ctgctgctat	tcctcaaccc	agatgcgttc	480
tgggggcccc	aggcctgcac	ccgtttcttc	tccogcatca	cgaaggccaa	tgtggacctg	540
ctcccgaggg	gggctcccga	gcgacagcgg	ctgctgcctg	cggctctggc	ctgctggggg	600
gtgcgggggt	ctctgctgag	cgaggctgat	gtgcgggctc	tgggaggcct	ggcttgcgac	660
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ccgggacccc	tggaccagga	ccagcaggag	gcagccaggg	cggctctgca	gggcggggga	780
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ctgcccgtgc	tgggccagcc	catcatccgc	agcatcccgc	agggcatcgt	ggcgcgctgg	900
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cggttccggc	gggaagtgga	gaagacagcc	tgtccttcag	gcaagaaggc	ccgcgagata	1020
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ctaaagcata	aactggatga	gctctaccca	caaggttacc	ccgagtctgt	gatccagcac	1200
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<210> 193
 <211> 702
 <212> PRT
 <213> Homo sapiens

<400> 193

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		20					25						30		
Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu
		35					40					45			
Asp	Gly	Val	Leu	Ala	Asn	Pro	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg
	50				55						60				
Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu
65					70					75					80
Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu
			85					90						95	
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro
		100						105					110		
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro
		115					120					125			
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile
	130					135					140				
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln
145					150					155					160
Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu
			165					170						175	
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu
		180						185					190		
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu
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Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg
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225					230					235					240
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly
			245						250					255	
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg
		260						265					270		
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile
		275					280					285			
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser
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Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys
305					310					315					320
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met
			325					330						335	
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu
			340					345					350		
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val
		355					360						365		
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile
	370					375					380				
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu
385					390					395					400
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Ala	Pro	Arg	Arg	Pro	Leu
			405						410					415	

198

Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
 420 425 430
 Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
 435 440 445
 Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
 450 455 460
 Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
 465 470 475 480
 Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
 485 490 495
 Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
 500 505 510
 Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
 515 520 525
 Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
 530 535 540
 Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
 545 550 555 560
 Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
 565 570 575
 Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
 580 585 590
 Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Gly Arg Gly Gly Gln
 595 600 605
 Ala Arg Ala Gly Gly Arg Ala Gly Gly Val Glu Val Gly Ala Leu Ser
 610 615 620
 His Pro Ser Leu Cys Arg Gly Pro Leu Gly Asp Ala Leu Pro Pro Arg
 625 630 635 640
 Thr Trp Thr Cys Ser His Arg Pro Gly Thr Ala Pro Ser Leu His Pro
 645 650 655
 Gly Leu Arg Ala Pro Leu Pro Cys Trp Pro Gln Pro Cys Trp Gly Ser
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 Pro Pro Gly Gln Glu Gln Ala Arg Val Ile Pro Val Pro Pro Gln Glu
 675 680 685
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<210> 194
 <211> 2135
 <212> DNA
 <213> Homo sapiens

<400> 194
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 tctgttggga ccccgcctt cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
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 gtgcgggggt ctctgctgag cgaggctgat gtgcgggctc tgggaggcct ggcttgcgac 660
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 ccgggacccc tggaccagga ccagcaggag gcagccagg cggctctgca gggcggggga 780
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199

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<210> 195

<211> 630

<212> PRT

<213> Homo sapiens

<400> 195

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              20              25              30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
              35              40              45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
              50              55              60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
              65              70              75              80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
              85              90              95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
              100             105             110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
              115             120             125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
              130             135             140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
              145             150             155             160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
              165             170             175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
              180             185             190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
              195             200             205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
              210             215             220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp

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200

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				245					250					255	
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg
			260					265					270		
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile
		275					280					285			
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser
	290					295					300				
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys
305					310					315					320
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met
				325					330					335	
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu
			340					345					350		
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val
	355						360					365			
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile
	370					375					380				
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu
385					390					395					400
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Ala	Pro	Arg	Arg	Pro	Leu
				405					410					415	
Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp	Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln
			420					425					430		
Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr
		435				440						445			
Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser
	450					455					460				
Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	Leu	Asp	Thr	Cys	Asp	Pro	Arg	Gln
465					470					475					480
Leu	Asp	Val	Leu	Tyr	Pro	Lys	Ala	Arg	Leu	Ala	Phe	Gln	Asn	Met	Asn
				485					490					495	
Gly	Ser	Glu	Tyr	Phe	Val	Lys	Ile	Gln	Ser	Phe	Leu	Gly	Gly	Ala	Pro
			500					505					510		
Thr	Glu	Asp	Leu	Lys	Ala	Leu	Ser	Gln	Gln	Asn	Val	Ser	Met	Asp	Leu
		515					520					525			
Ala	Thr	Phe	Met	Lys	Leu	Arg	Thr	Asp	Ala	Val	Leu	Pro	Leu	Thr	Val
	530					535					540				
Ala	Glu	Val	Gln	Lys	Leu	Leu	Gly	Pro	His	Val	Glu	Gly	Leu	Lys	Ala
545					550				555						560
Glu	Glu	Arg	His	Arg	Pro	Val	Arg	Asp	Trp	Ile	Leu	Arg	Gln	Arg	Gln
				565					570					575	
Asp	Asp	Leu	Asp	Thr	Leu	Gly	Leu	Gly	Leu	Gln	Gly	Gly	Ile	Pro	Asn
			580					585					590		
Gly	Tyr	Leu	Val	Leu	Asp	Leu	Ser	Val	Gln	Glu	Ala	Leu	Ser	Gly	Thr
		595					600					605			
Pro	Cys	Leu	Leu	Gly	Pro	Gly	Pro	Val	Leu	Thr	Val	Leu	Ala	Leu	Leu
	610					615					620				
Leu	Ala	Ser	Thr	Leu	Ala										
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<210> 196

<211> 2105

<212> DNA

<213> Homo sapiens

<400> 196

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<210> 197

<211> 620

<212> PRT

<213> Homo sapiens

<400> 197

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 20              25              30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
 35              40              45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
 50              55              60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
 65              70              75              80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
 85              90              95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
 100            105            110

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	130					135					140				
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln
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Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu
				165					170					175	
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu
		180						185					190		
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu
	195						200					205			
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg
	210					215					220				
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Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly
				245					250					255	
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg
		260						265					270		
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Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met
				325					330					335	
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu
		340						345					350		
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val
	355						360					365			
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile
	370					375					380				
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu
385					390					395					400
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Ala	Pro	Arg	Arg	Pro	Leu
				405					410					415	
Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp	Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln
		420						425					430		
Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr
	435						440					445			
Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser
	450					455					460				
Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	Leu	Asp	Thr	Cys	Asp	Pro	Arg	Gln
465					470					475					480
Leu	Asp	Val	Leu	Tyr	Pro	Lys	Ala	Arg	Leu	Ala	Phe	Gln	Asn	Met	Asn
				485					490					495	
Gly	Ser	Glu	Tyr	Phe	Val	Lys	Ile	Gln	Ser	Phe	Leu	Gly	Gly	Ala	Pro
			500					505					510		
Thr	Glu	Asp	Leu	Lys	Ala	Leu	Ser	Gln	Gln	Asn	Val	Ser	Met	Asp	Leu
	515						520					525			
Ala	Thr	Phe	Met	Lys	Leu	Arg	Thr	Asp	Ala	Val	Leu	Pro	Leu	Thr	Val
	530					535					540				
Ala	Glu	Val	Gln	Lys	Leu	Leu	Gly	Pro	His	Val	Glu	Gly	Leu	Lys	Ala
545					550					555					560
Glu	Glu	Arg	His	Arg	Pro	Val	Arg	Asp	Trp	Ile	Leu	Arg	Gln	Arg	Gln
				565					570					575	

203

Asp	Asp	Leu	Asp	Thr	Leu	Gly	Leu	Gly	Leu	Gln	Gly	Gly	Ile	Pro	Asn
			580					585					590		
Gly	Tyr	Leu	Val	Leu	Asp	Leu	Ser	Val	Gln	Gly	Pro	Gly	Pro	Val	Leu
		595					600					605			
Thr	Val	Leu	Ala	Leu	Leu	Leu	Ala	Ser	Thr	Leu	Ala				
	610					615					620				

<210> 198
 <211> 2193
 <212> DNA
 <213> Homo sapiens

<400> 198
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 tcctgtggga ccccgccct cggcagocct ctgttcctgc tcttcagcct cggatgggtg 180
 cagccctcga ggacctggc tggagagaca gggcaggagg ctgcaccctt ggacggagtc 240
 ctggccaacc cacctaaccat ttccagcctc tcccctcgcc aactccttgg cttcccgtgt 300
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 aagaatgtca agctctcaac agagcagctg cgctgtctgg ctaccggct ctctgagccc 420
 cccgaggacc tggacgccct cccattggac ctgctgctat tcctcaaccc agatgcgttc 480
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 ctcccagagg gggctcccg ggcacagcgg ctgctgcctg cggctctggc ctgctggggt 600
 gtgcgggggt ctctgctgag cgaggctgat gtgcgggctc tgggaggcct ggcttgcgac 660
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 ccgggacccc tggaccagga ccagcaggag gcagccaggg cggctctgca gggcggggga 780
 cccccctacg gcccccgctc gacatggtct gtctccacga tggacgctct gcggggcctg 840
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 gacgagagcc tcatcttcta caagaagtgg gagctggaag cctgcgtgga tgcggccctg 1080
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<210> 199
 <211> 694
 <212> PRT
 <213> Homo sapiens

<400> 199

Met	Ala	Leu	Pro	Thr	Ala	Arg	Pro	Leu	Leu	Gly	Ser	Cys	Gly	Thr	Pro	1	5	10	15
Ala	Leu	Gly	Ser	Leu	Leu	Phe	Leu	Leu	Phe	Ser	Leu	Gly	Trp	Val	Gln	20	25	30	
Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu	35	40	45	
Asp	Gly	Val	Leu	Ala	Asn	Pro	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg	50	55	60	
Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu	65	70	75	80
Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu	85	90	95	
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro	100	105	110	
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro	115	120	125	
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile	130	135	140	
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln	145	150	155	160
Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu	165	170	175	
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu	180	185	190	
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu	195	200	205	
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg	210	215	220	
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp	225	230	235	240
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly	245	250	255	
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg	260	265	270	
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile	275	280	285	
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser	290	295	300	
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys	305	310	315	320
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met	325	330	335	
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu	340	345	350	
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val	355	360	365	
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile	370	375	380	
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu	385	390	395	400
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp	405	410	415	
Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	420	425	430	
Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	435	440	445	
Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser	Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	450	455	460	

205

Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
 465 470 475 480
 Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
 485 490 495
 Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
 500 505 510
 Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
 515 520 525
 Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
 530 535 540
 Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
 545 550 555 560
 Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
 565 570 575
 Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
 580 585 590
 Val Gln Gly Gly Arg Gly Gly Gln Ala Arg Ala Gly Gly Arg Ala Gly
 595 600 605
 Gly Val Glu Val Gly Ala Leu Ser His Pro Ser Leu Cys Arg Gly Pro
 610 615 620
 Leu Gly Asp Ala Leu Pro Pro Arg Thr Trp Thr Cys Ser His Arg Pro
 625 630 635 640
 Gly Thr Ala Pro Ser Leu His Pro Gly Leu Arg Ala Pro Leu Pro Cys
 645 650 655
 Trp Pro Gln Pro Cys Trp Gly Ser Pro Pro Gly Gln Glu Gln Ala Arg
 660 665 670
 Val Ile Pro Val Pro Pro Gln Glu Asn Ser Arg Ser Val Asn Gly Asn
 675 680 685
 Met Pro Pro Ala Asp Thr
 690

<210> 200

<211> 2081

<212> DNA

<213> Homo sapiens

<400> 200

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 tctgtggga ccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
 cagccctcga ggaccctggc tggagagaca gggcaggagg ctgcaccctt ggacggagtc 240
 ctggccaacc caccatacat ttccagcctc tcccctcgcc aactccttgg cttcccgtgt 300
 gcgagggtgt ccggcctgag cacggagcgt gtccgggagc tggctgtggc cttggcacag 360
 aagaatgtca agctctcaac agagcagctg cgctgtcttg ctcaccggct ctctgagccc 420
 cccgaggacc tggacgcctt cccattggac ctgctgctat tcctcaacc agatgcgttc 480
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 ccgggacccc tggaccagga ccagcaggag gcagccaggg cggctctgca gggcggggga 780
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 ctggccaccc agatggaccg cgtgaacgcc atccccttca cctacgagca gctggacgtc 1140
 ctaaagcata aactggtatga gctctaccca caaggttacc ccgagtctgt gatccagcac 1200

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ctgggctacc tcttcctcaa gatgagccct gaggacattc gcaagtggaa tgtgacgtcc 1260
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cagctggacg tcctctatcc caaggcccgc cttgctttcc agaacadgaa cgggtccgaa 1560
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gcctgagggc cccactccct tgctggcccc agcctgctg gggatccccg cctggccagg 1980
agcaggcacg ggtgatcccc gttccacccc aagagaactc gcgctcagta aacgggaaca 2040
tgccccctgc agacacgtaa aaaaaaaaaa aaaaaaaaaa a 2081

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<210> 201

<211> 612

<212> PRT

<213> Homo sapiens

<400> 201

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Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
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Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
  20          25          30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
  35          40          45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
  50          55          60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
  65          70          75          80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
  85          90          95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
  100         105         110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
  115         120         125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
  130         135         140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
  145         150         155         160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
  165         170         175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
  180         185         190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
  195         200         205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
  210         215         220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
  225         230         235         240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
  245         250         255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
  260         265         270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
  275         280         285

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207

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
 290 295 300
 Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
 305 310 315 320
 Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
 325 330 335
 Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
 340 345 350
 Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
 355 360 365
 Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
 370 375 380
 Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
 385 390 395 400
 Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
 405 410 415
 Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
 420 425 430
 Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
 435 440 445
 Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
 450 455 460
 Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
 465 470 475 480
 Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
 485 490 495
 Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
 500 505 510
 Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
 515 520 525
 Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
 530 535 540
 Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
 545 550 555 560
 Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
 565 570 575
 Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
 580 585 590
 Val Gln Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu Leu Ala
 595 600 605
 Ser Thr Leu Ala
 610

<210> 202

<211> 1195

<212> DNA

<213> Homo sapiens

<400> 202

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 gaccgcgtga acgccatccc ctacacctac gagcagctgg acgtcctaaa gcataaactg 180
 gatgagctct acccacaagg ttaccccgag tctgtgatcc agcacctggg ctacctcttc 240
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 cgctttgtga agggaagggg ccagctagac aaagacaccc tagacaccct gaccgccttc 420
 taccctgggt acctgtgctc cctcagcccc gaggagctga gctccgtgcc cccagcagc 480

208

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atctgggcg ttagggccca ggacctggac acgtgtgacc caaggcagct ggacgtcctc 540
tatcccaagg cccgccttgc tttccagaac atgaacgggt cogaatactt cgtgaagatc 600
cagtccttcc tgggtggggc cccacaggag gatttgaagg cgctcagtca gcagaatgtg 660
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<210> 203

<211> 398

<212> PRT

<213> Homo sapiens

<400> 203

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Glu Ser Leu Ile Phe Tyr Lys Lys Trp Glu Leu Glu Ala Cys Val Asp
          20          25          30
Ala Ala Leu Leu Ala Thr Gln Met Asp Arg Val Asn Ala Ile Pro Phe
          35          40          45
Thr Tyr Glu Gln Leu Asp Val Leu Lys His Lys Leu Asp Glu Leu Tyr
          50          55          60
Pro Gln Gly Tyr Pro Glu Ser Val Ile Gln His Leu Gly Tyr Leu Phe
65          70          75          80
Leu Lys Met Ser Pro Glu Asp Ile Arg Lys Trp Asn Val Thr Ser Leu
          85          90          95
Glu Thr Leu Lys Ala Leu Leu Glu Val Asn Lys Gly His Glu Met Ser
          100          105          110
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
          115          120          125
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
130          135          140
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
145          150          155          160
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
          165          170          175
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
          180          185          190
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
          195          200          205
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
210          215          220
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
225          230          235          240
Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
          245          250          255
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
260          265          270
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
275          280          285
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Gly Arg Gly Gly Gln
290          295          300
Ala Arg Ala Gly Gly Arg Ala Gly Gly Val Glu Val Gly Ala Leu Ser

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209

305					310					315					320
His	Pro	Ser	Leu	Cys	Arg	Gly	Pro	Leu	Gly	Asp	Ala	Leu	Pro	Pro	Arg
				325					330					335	
Thr	Trp	Thr	Cys	Ser	His	Arg	Pro	Gly	Thr	Ala	Pro	Ser	Leu	His	Pro
			340					345					350		
Gly	Leu	Arg	Ala	Pro	Leu	Pro	Cys	Trp	Pro	Gln	Pro	Cys	Trp	Gly	Ser
			355				360					365			
Pro	Pro	Gly	Gln	Glu	Gln	Ala	Arg	Val	Ile	Pro	Val	Pro	Pro	Gln	Glu
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<210> 204
 <211> 2085
 <212> DNA
 <213> Homo sapiens

<400> 204

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cctgctgggg	atccccgcct	ggccaggagc	aggcacgggt	gatccccggt	ccaccccaag	2040
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<210> 205
 <211> 622
 <212> PRT

<213> Homo sapiens

<400> 205

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			20					25					30		
Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu
		35					40					45			
Asp	Gly	Val	Leu	Ala	Asn	Pro	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg
	50					55					60				
Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu
65					70					75					80
Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu
				85					90					95	
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro
			100					105					110		
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro
	115						120					125			
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile
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Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln
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Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu
				165				170						175	
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu
			180					185					190		
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu
	195						200						205		
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg
	210					215				220					
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp
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Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly
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Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg
			260					265					270		
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Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser
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Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met
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Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu
			340					345					350		
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val
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Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile
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Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu
385					390					395					400
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp
				405					410					415	
Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr
			420					425					430		
Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu

211

435	440	445
Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp		
450	455	460
Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala		
465	470	475
Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile		
	485	490
Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser		
	500	505
Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr		
	515	520
Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly		
	530	535
Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg		
545	550	555
Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu		
	565	570
Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser		
	580	585
Val Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro		
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Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala		
610	615	620

<210> 206
 <211> 2111
 <212> DNA
 <213> Homo sapiens

<400> 206
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212

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<210> 207
<211> 2107
<212> DNA
<213> Homo sapiens

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<210> 208
<211> 628
<212> PRT
<213> Homo sapiens

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<400> 208

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		20						25					30		
Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Thr	Glu	Ser	Ala	Pro	Leu	Gly	Gly
		35					40					45			
Val	Leu	Thr	Thr	Pro	His	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg	Gln	Leu
	50					55					60				
Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu	Arg	Val
65					70					75					80
Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu	Ser	Thr
				85					90					95	
Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro	Glu	Asp
			100					105					110		
Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro	Asp	Ala
		115					120					125			
Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile	Thr	Lys
	130					135					140				
Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln	Arg	Leu
145					150					155					160
Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu	Leu	Ser
			165						170					175	
Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu	Pro	Gly
			180					185					190		
Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu	Val	Ser
		195					200					205			
Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg	Ala	Ala
	210					215					220				
Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp	Ser	Val
225					230					235					240
Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly	Gln	Pro
				245					250					255	
Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg	Gln	Arg
			260					265					270		
Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile	Leu	Arg
		275					280					285			
Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser	Gly	Lys
	290					295					300				
Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys	Trp	Glu
305					310					315					320
Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met	Asp	Arg
				325					330					335	
Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu	Lys	His
		340						345				350			
Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val	Ile	Gln
		355					360					365			
His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile	Arg	Lys
	370					375					380				
Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu	Val	Asp
385					390					395					400
Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Ala	Pro	Arg	Arg	Pro	Leu	Pro	Gln
				405					410					415	
Val	Ala	Thr	Leu	Ile	Asp	Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	Leu	Asp
			420					425					430		
Lys	Asp	Thr	Leu	Asp	Thr	Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	Leu	Cys
		435					440					445			
Ser	Leu	Ser	Pro	Glu	Glu	Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser	Ile	Trp

214

450	455	460
Ala Val Arg Pro Gln Asp	Leu Asp Thr Cys Asp	Pro Arg Gln Leu Asp
465	470	475
Val Leu Tyr Pro Lys Ala	Arg Leu Ala Phe Gln	Asn Met Asn Gly Ser
485	490	495
Glu Tyr Phe Val Lys Ile	Gln Ser Phe Leu Gly	Gly Ala Pro Thr Glu
500	505	510
Asp Leu Lys Ala Leu Ser	Gln Gln Asn Val Ser	Met Asp Leu Ala Thr
515	520	525
Phe Met Lys Leu Arg Thr	Asp Ala Val Leu Pro	Leu Thr Val Ala Glu
530	535	540
Val Gln Lys Leu Leu Gly	Pro His Val Glu Gly	Leu Lys Ala Glu Glu
545	550	555
Arg His Arg Pro Val Arg	Asp Trp Ile Leu Arg	Gln Arg Gln Asp Asp
565	570	575
Leu Asp Thr Leu Gly Leu	Gly Leu Gln Gly Gly	Ile Pro Asn Gly Tyr
580	585	590
Leu Val Leu Asp Leu Ser	Val Gln Glu Thr Leu	Ser Gly Thr Pro Cys
595	600	605
Leu Leu Gly Pro Gly Pro	Val Leu Thr Val Leu	Ala Leu Leu Leu Ala
610	615	620
Ser Thr Leu Ala		
625		

<210> 209

<211> 2316

<212> DNA

<213> Homo sapiens

<400> 209

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215

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<212> PRT
<213> Homo sapiens

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Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
 35           40           45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
 50           55           60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
 65           70           75           80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
 85           90           95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100          105          110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
115          120          125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
130          135          140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145          150          155          160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
165          170          175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
180          185          190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
195          200          205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
210          215          220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225          230          235          240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
245          250          255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
260          265          270

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216

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
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 Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
 290 295 300
 Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
 305 310 315 320
 Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
 325 330 335
 Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
 340 345 350
 Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
 355 360 365
 Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
 370 375 380
 Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
 385 390 395 400
 Val Asp Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu
 405 410 415
 Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
 420 425 430
 Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
 435 440 445
 Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
 450 455 460
 Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
 465 470 475 480
 Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
 485 490 495
 Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
 500 505 510
 Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
 515 520 525
 Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
 530 535 540
 Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
 545 550 555 560
 Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
 565 570 575
 Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
 580 585 590
 Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Xaa Xaa Leu Ser Gly Thr
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 625 630

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 <212> DNA
 <213> Homo sapiens

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ccagtcacca ggccagccct gggctccacc accccgccag cccacgatgt cacctcagcc 420
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<210> 212

<211> 515

<212> PRT

<213> Homo sapiens

<400> 212

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  20          25          30
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
  35          40          45
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
  50          55          60
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
  65          70          75          80
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
  85          90          95
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
  100          105          110
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro
  115          120          125
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
  130          135          140
Arg Pro Pro Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
  145          150          155          160
Ala Pro Asp Thr Arg Pro Pro Pro Gly Ser Thr Ala Pro Ala Ala His
  165          170          175
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
  180          185          190
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu
  195          200          205

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218

Ala Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly Ser
 210 215 220
 Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg
 225 230 235 240
 Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro Ser
 245 250 255
 His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr
 260 265 270
 Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser Ser
 275 280 285
 Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe
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 Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp
 305 310 315 320
 Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met
 325 330 335
 Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile
 340 345 350
 Lys Phe Arg Pro Gly Ser Val Val Gln Leu Thr Leu Ala Phe Arg
 355 360 365
 Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr
 370 375 380
 Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser
 385 390 395 400
 Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val
 405 410 415
 Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala
 420 425 430
 Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg
 435 440 445
 Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His
 450 455 460
 Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro
 465 470 475 480
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 Ala Asn Leu
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<210> 213

<211> 5793

<212> DNA

<213> Homo sapiens

<400> 213

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<211> 1783

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

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<223> Xaa = Any Amino Acid

<400> 214

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Asn Phe Thr Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro
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Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Val		590

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Thr Thr Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile
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Thr Asn Leu Arg Tyr Glu Glu Asn Met His His Pro Gly Ser Arg Lys
130          135          140
Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe
145          150          155          160
Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu
165          170          175
Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp Ala Ile Cys
180          185          190
Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln Leu
195          200          205
Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro
210          215          220
Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr Gln Arg

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Ser	Ser	Val	Pro	Thr	Thr	Ser	Ile	Pro	Gly	Thr	Pro	Thr	Val	Asp	Leu
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Gly	Thr	Ser	Gly	Thr	Pro	Val	Ser	Lys	Pro	Gly	Pro	Ser	Ala	Ala	Ser
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Pro	Leu	Leu	Val	Leu	Phe	Thr	Leu	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Arg
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Tyr	Glu	Glu	Asn	Met	Gln	His	Pro	Gly	Ser	Arg	Lys	Phe	Asn	Thr	Thr
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Glu	Arg	Val	Leu	Gln	Gly	Leu	Leu	Arg	Ser	Leu	Phe	Lys	Ser	Thr	Ser
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Val	Gly	Pro	Leu	Tyr	Ser	Gly	Cys	Arg	Leu	Thr	Leu	Leu	Arg	Pro	Glu
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Lys	Asp	Gly	Thr	Ala	Thr	Gly	Val	Asp	Ala	Ile	Cys	Thr	His	His	Pro
			340					345					350		
Asp	Pro	Lys	Ser	Pro	Arg	Leu	Asp	Arg	Glu	Gln	Leu	Tyr	Trp	Glu	Leu
			355				360					365			
Ser	Gln	Leu	Thr	His	Asn	Ile	Thr	Glu	Leu	Gly	His	Tyr	Ala	Leu	Asp
	370					375					380				
Asn	Asp	Ser	Leu	Phe	Val	Asn	Gly	Phe	Thr	His	Arg	Ser	Ser	Val	Ser
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Thr	Thr	Ser	Thr	Pro	Gly	Thr	Pro	Thr	Val	Tyr	Leu	Gly	Ala	Ser	Lys
			405						410					415	
Thr	Pro	Ala	Ser	Ile	Phe	Gly	Pro	Ser	Ala	Ala	Ser	His	Leu	Leu	Ile
			420					425					430		
Leu	Phe	Thr	Leu	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Arg	Tyr	Glu	Glu	Asn
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Met	Trp	Pro	Gly	Ser	Arg	Lys	Phe	Asn	Thr	Thr	Glu	Arg	Val	Leu	Gln
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Gly	Leu	Leu	Arg	Pro	Leu	Phe	Lys	Asn	Thr	Ser	Val	Gly	Pro	Leu	Tyr
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Ser	Gly	Ser	Arg	Leu	Thr	Leu	Leu	Arg	Pro	Glu	Lys	Asp	Gly	Glu	Ala
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Gly	Leu	Asp	Arg	Glu	Gln	Leu	Tyr	Leu	Glu	Leu	Ser	Gln	Leu	Thr	His
			515				520					525			
Ser	Ile	Thr	Glu	Leu	Gly	Pro	Thr	Thr	Leu	Asp	Arg	Asp	Ser	Leu	Tyr
	530					535					540				
Val	Asn	Gly	Phe	Thr	His	Arg	Ser	Ser	Val	Pro	Thr	Thr	Ser	Thr	Gly
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Val	Val	Ser	Glu	Glu	Pro	Phe	Thr	Leu	Asn	Phe	Thr	Ile	Asn	Asn	Leu
			565						570					575	
Arg	Tyr	Met	Ala	Asp	Met	Gly	Gln	Pro	Gly	Ser	Leu	Lys	Phe	Asn	Ile
			580					585							

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Ser Glu Ala Thr Thr	Ala Met Gly Tyr His	Leu Lys Thr Leu Thr Leu		
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Asn Phe Thr Ile Ser	Asn Leu Gln Tyr Ser	Pro Asp Met Gly Lys Gly		
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Ser Ala Thr Phe Asn	Ser Thr Glu Gly Val	Leu Gln His Leu Leu Arg		
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Pro Leu Phe Gln Lys	Ser Ser Met Gly Pro	Phe Tyr Leu Gly Cys Gln		
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Leu Ile Ser Leu Arg	Pro Glu Lys Asp Gly	Ala Ala Thr Gly Val Asp		
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Thr Thr Cys Thr Tyr	His Pro Asp Pro Val	Gly Pro Gly Leu Asp Ile		
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Gln Gln Leu Tyr Trp	Glu Leu Ser Gln Leu	Thr His Gly Val Thr Gln		
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Leu Gly Phe Tyr Val	Leu Asp Arg Asp Ser	Leu Phe Ile Asn Gly Tyr		
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Ala Pro Gln Asn Leu	Ser Ile Arg Gly Glu	Tyr Gln Ile Asn Phe His		
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Ile Val Asn Trp Asn	Leu Ser Asn Pro Asp	Pro Thr Ser Ser Glu Tyr		
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Ile Thr Leu Leu Arg	Asp Ile Gln Asp Lys	Val Thr Thr Leu Tyr Lys		
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Gly Ser Gln Leu His	Asp Thr Phe Arg Phe	Cys Leu Val Thr Asn Leu		
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Ala Ser Phe His Trp	Leu Gly Ser Thr Tyr	Gln Leu Val Asp Ile His		
	930	935	940	
Val Thr Glu Met Glu	Ser Ser Val Tyr Gln	Pro Thr Ser Ser Ser Ser		
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Thr Gln His Phe Tyr	Pro Asn Phe Thr Ile	Thr Asn Leu Pro Tyr Ser		
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Asn Ile Glu Asp Ala	Leu Asn Gln Leu Phe	Arg Asn Ser Ser Ile Lys		
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Ser Tyr Phe Ser Asp	Cys Gln Val Ser Thr	Phe Arg Ser Val Pro Asn		
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Arg His His Thr Gly	Val Asp Ser Leu Cys	Asn Phe Ser Pro Leu Ala		
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Arg Arg Val Asp Arg	Val Ala Ile Tyr Glu	Glu Phe Leu Arg Met Thr		
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Arg Asn Gly Thr Gln	Leu Gln Asn Phe Thr	Leu Asp Arg Ser Ser Val		
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Leu Val Asp Gly Tyr	Ser Pro Asn Arg Asn	Glu Pro Leu Thr Gly Asn		
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Ser Asp Leu Pro Phe	Trp Ala Val Ile Phe	Ile Gly Leu Ala Gly Leu		
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Leu Gly Leu Ile Thr	Cys Leu Ile Cys Gly	Val Leu Val Thr Thr Arg		
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Arg Arg Lys Lys Glu	Gly Glu Tyr Asn Val	Gln Gln Gln Cys Pro Gly		
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Tyr Tyr Gln Ser His	Leu Asp Leu Glu Asp	Leu Gln		
	1140	1145		

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<400> 217

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Leu	Asp	Arg	Asp	Ser	Leu	Tyr	Val	Asn	Gly	Phe	Asn	Pro	Trp	Ser	Ser
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Ser	Gly	Thr	Pro	Ser	Ser	Leu	Pro	Gly	His	Thr	Ala	Pro	Val	Pro	Leu
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Glu	Asn	Met	Gln	His	Pro	Gly	Ser	Arg	Lys	Phe	Asn	Thr	Thr	Glu	Arg
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Val	Leu	Gln	Gly	Leu	Leu	Lys	Pro	Leu	Phe	Lys	Ser	Thr	Ser	Val	Gly
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Thr	Gly	Pro	Gly	Leu	Asp	Arg	Glu	Arg	Leu	Tyr	Trp	Glu	Leu	Ser	Gln
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Ser	Ile	Pro	Gly	Thr	Ser	Ala	Val	His	Leu	Glu	Thr	Ser	Gly	Thr	Pro
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Ala	Ser	Leu	Pro	Gly	His	Thr	Ala	Pro	Gly	Pro	Leu	Leu	Val	Pro	Phe
225					230					235					240
Thr	Leu	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Gln	Tyr	Glu	Glu	Asp	Met	Arg
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His	Pro	Gly	Ser	Arg	Lys	Phe	Asn	Thr	Thr	Glu	Arg	Val	Leu	Gln	Gly
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Leu	Leu	Lys	Pro	Leu	Phe	Lys	Ser	Thr	Ser	Val	Gly	Pro	Leu	Tyr	Ser
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Leu	Asp	Arg	Glu	Gln	Leu	Tyr	Trp	Glu	Leu	Ser	Lys	Leu	Thr	Arg	Gly
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Thr	Ser	Thr	Val	His	Leu	Gly	Thr	Ser	Glu	Thr	Pro	Ser	Ser	Leu	Pro
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Arg	Pro	Ile	Val	Pro	Gly	Pro	Leu	Leu	Val	Pro	Phe	Thr	Leu	Asn	Phe
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Thr	Ile	Thr	Asn	Leu	Gln	Tyr	Glu	Glu	Ala	Met	Arg	His	Pro	Gly	Ser

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Leu Leu Arg Pro Val Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser						
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Gly Cys Arg Leu Thr Leu Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr						
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Lys Val Asp Ala Ile Cys Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly						
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Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser						
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Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val						
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Asn Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly						
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Thr Pro Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Val Ser Lys Pro						
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Gly Pro Ser Ala Ala Ser Pro Leu Leu Val Leu Phe Thr Leu Asn Phe						
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Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Ser						
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Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu						
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Thr Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp Ala						
	1075		1080			1085
Ile Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu						
	1090		1095			1100
Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu						
1105		1110		1115		1120
Gly Pro Tyr Ala Leu Asp Asn Asp Ser Leu Phe Val Asn Gly Phe Thr						
	1125		1130			1135
His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr Pro Thr Val						
	1140		1145			1150
Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser Ile Phe Gly Pro Ser Ala						
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Ala Ser His Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn						
	1170		1175			1180
Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys Phe Asn Thr						
1185		1190		1195		1200
Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr						
	1205		1210			1215
Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro						
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Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg						
	1235		1240			1245
Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu						
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Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu						
1265		1270		1275		1280
Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser Ser Val						
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Pro Thr Thr Ser Thr Gly Val Val Ser Glu Glu Pro Phe Thr Leu Asn						
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Phe Thr Ile Asn Asn Leu Arg Tyr Met Ala Asp Met Gly Gln Pro Gly						
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Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Gln His Leu Leu Ser						

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Val Ile Ala Leu Arg Ser Val Lys Asn Gly Ala Glu Thr Arg Val Asp		1360
	1365	1370
Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile		1375
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Lys Gln Val Phe His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg		1390
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Leu Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr		1405
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Asn Glu Pro Gly Pro Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr		1420
1425	1430	1435
Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His		1440
	1445	1450
Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser		1455
	1460	1465
Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val		1470
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Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly		1500
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Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu		1535
	1540	1545
Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser		1550
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Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu		1565
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Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp		1580
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Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys		1600
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Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe		1615
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Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys		1630
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Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe		1645
	1650	1655
Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr		1660
1665	1670	1675
Gln Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln		1680
	1685	1690
Pro Thr Ser Ser Ser Thr Gln His Phe Tyr Pro Asn Phe Thr Ile		1695
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Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn		1710
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Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe		1725
	1730	1735
Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr		1740
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Phe Arg Ser Val Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys		1760
	1765	1770
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu		1775
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Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr		1790

233

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Ile Gly Leu Ala Gly Leu Leu Gly	Leu Ile Thr Cys	Leu Ile Cys Gly
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Val Leu Val Thr Thr Arg Arg Arg	Lys Lys Glu Gly Glu Tyr	Asn Val
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235

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238

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 <212> DNA
 <213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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Leu Leu Pro Ser Tyr Ser Thr Ala Thr Leu Ile Asp Glu Pro Thr Glu
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Val Asp Asp Pro Trp Asn Leu Pro Thr Leu Gln Asp Ser Gly Ile Lys
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Trp Ser Glu Arg Asp Thr Lys Gly Lys Ile Leu Cys Phe Phe Gln Gly
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Ile Gly Arg Leu Ile Leu Leu Leu Gly Phe Leu Tyr Phe Phe Val Cys
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Gly Leu Val Ile Gly Val Leu Val Thr Val Leu Val Gln Ser Ser Ser
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165          170          175
Val Arg Ala Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly Thr Ser
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Phe Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe Asn Trp

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240

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Cys Thr Ser Pro Ser	Leu Cys Trp Thr Asp	Gly Ile Gln Asn Trp Thr
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Met Lys Asn Val Thr	Tyr Lys Glu Asn Ile Ala	Lys Cys Gln His Ile
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Val Phe Tyr Leu Ile	Ile Phe Phe Phe Leu	Ile Pro Leu Thr Val Phe
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Gly Leu Ser Leu Ala	Gly Trp Arg Val Leu	Val Gly Val Gly Val Pro
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565	570	575
Arg Cys Pro Arg Val	Leu Pro Lys Lys Leu	Gln Asn Trp Asn Phe Leu
580	585	590
Pro Leu Trp Met Arg	Ser Leu Lys Pro Trp	Asp Ala Val Val Ser Lys
595	600	605
Phe Thr Gly Cys Phe	Gln Met Arg Cys Cys	Cys Cys Cys Arg Val Cys
610	615	620
Cys Arg Ala Cys Cys	Leu Leu Cys Gly Cys	Pro Lys Cys Cys Arg Cys
625	630	635
Ser Lys Cys Cys Glu	Asp Leu Glu Glu Ala	Gln Glu Gly Gln Asp Val
645	650	655
Pro Val Lys Ala Pro	Glu Thr Phe Asp Asn	Ile Thr Ile Ser Arg Glu
660	665	670
Ala Gln Gly Glu Val	Pro Ala Ser Asp Ser	Lys Thr Glu Cys Thr Ala

241

675 680 685

Leu

<210> 222
 <211> 771
 <212> DNA
 <213> Homo sapiens

<400> 222
 gccgctgagc cataatggag atatcaatgc ctccacctca gatatatgta gaaaaaactc 60
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 gatccggatt caccattgtt cagagaagaa aactacgcct cagccctgag caatgtagta 180
 acttttatgt ggaaaagtat ggaaaaatgt ttttcccaa ctaacagct tacatgagtt 240
 ctggaccact tgtcgccatg atattagcta gacataaagc catctcttat tggttagaac 300
 ttttgggacc aaataatagc ttagtagcga aggagacaca tccagacagt ctgagggcaa 360
 tttatggcac agatgaccta aggaatgcac ttcattggag taatgacttt gctgctgcgg 420
 aaagagaaat acgttttatg tttcctgaag tgattgttga gccattcca attggacaag 480
 ctgctaagga ctattttaa tttacatataa tgccaactct gcttgaagga ctcacagagc 540
 tttgtaagca aaaaccagca gaccctttga tttggctagc tgattggctg ctgaaaaata 600
 atcctaacaa acccaaactt tgtcaccatc caattgtaga agaaccctat taaaaaaaaa 660
 atcctcgaaa gaacaaatca tgaactatct tattataaaa ggctgtactt ctactgtttg 720
 agaaaattat ttctagggtt taagtaacta ccagtaaaat aaatttattt c 771

<210> 223
 <211> 212
 <212> PRT
 <213> Homo sapiens

<400> 223
 Met Glu Ile Ser Met Pro Pro Pro Gln Ile Tyr Val Glu Lys Thr Leu
 1 5 10 15
 Ala Ile Ile Lys Pro Asp Ile Val Asp Lys Glu Glu Glu Ile Gln Asp
 20 25 30
 Ile Ile Leu Arg Ser Gly Phe Thr Ile Val Gln Arg Arg Lys Leu Arg
 35 40 45
 Leu Ser Pro Glu Gln Cys Ser Asn Phe Tyr Val Glu Lys Tyr Gly Lys
 50 55 60
 Met Phe Phe Pro Asn Leu Thr Ala Tyr Met Ser Ser Gly Pro Leu Val
 65 70 75 80
 Ala Met Ile Leu Ala Arg His Lys Ala Ile Ser Tyr Trp Leu Glu Leu
 85 90 95
 Leu Gly Pro Asn Asn Ser Leu Val Ala Lys Glu Thr His Pro Asp Ser
 100 105 110
 Leu Arg Ala Ile Tyr Gly Thr Asp Asp Leu Arg Asn Ala Leu His Gly
 115 120 125
 Ser Asn Asp Phe Ala Ala Ala Glu Arg Glu Ile Arg Phe Met Phe Pro
 130 135 140
 Glu Val Ile Val Glu Pro Ile Pro Ile Gly Gln Ala Ala Lys Asp Tyr
 145 150 155 160
 Leu Asn Leu His Ile Met Pro Thr Leu Leu Glu Gly Leu Thr Glu Leu
 165 170 175
 Cys Lys Gln Lys Pro Ala Asp Pro Leu Ile Trp Leu Ala Asp Trp Leu
 180 185 190
 Leu Lys Asn Asn Pro Asn Lys Pro Lys Leu Cys His His Pro Ile Val
 195 200 205
 Glu Glu Pro Tyr

210

<210> 224
 <211> 3463
 <212> DNA
 <213> Homo sapiens

<400> 224

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atggctgagc cgactagtga tttcagagact cctatcgggt ggcatgcgtc tcccagactg 60
actcccacgt tagggccctt gagcgacact gcccgcgcgc gggacagggt gatgttctgg 120
gcaatgctgc cgccaccgcc accaccactt acgtcctcgc ttcccgcagc cgggtcaaag 180
ccttcctctg agtcgcagcc ccccatggag gccagttctc tcccgggggc tccgcccccc 240
ttcgacgccc agattcttcc cggggcgcaa cccccttcg acgcccagtc tccccttgat 300
tctcagcctc aaccagcgg ccagccttgg aatttccatg cttccacatc gtgggtattgg 360
agacagtctt ctgatagggt tcctcggeat cagaagtcct tcaaccctgc agttaaaaaat 420
tcttattatc cacgaaagta tgatgcaaaa ttcacagact tcagcttacc tcccagtaga 480
aaacagaaaa aaaagaaaag aaaggaacca gtttttctact ttttttgtga tacctgtgat 540
cgtgggtttta aaaatcaaga aaagtatgac aaacacatgt ctgaacatac aaaatgccct 600
gaatttagatt gctcttttac tgcacacgag aagattgtcc agttccattg gagaaatatg 660
catgctcctg gcatgaagaa gatcaagtta gacactccag aggaaattgc acggtggagg 720
gaagaaagaa ggaaaaacta tccaactctg gccaatattg aaaggaagaa gaagttaaaa 780
cttgaaaagg agaagagagg agcagtattg acaacaacac aatatggcaa gatgaagggg 840
atgtccagac attcacaagt ggcaaagatc agaagtcctg gcaagaatca caaatggaaa 900
aacgacaatt ctagacagag agcagtcact ggatcaggca gtcacttgtg tgatttgaag 960
ctagaagggt caccggaggc aaatgcagat cctcttggtg ttttgataaa cagtgtattct 1020
gagtcctgata aggaggagaa accacaacat tctgtgatac ccaaggaagt gacaccagcc 1080
cratgccrac taatgagtag ctatggcagt ctttcagggt cagagagtga gccagaagaa 1140
actcccatca agactgaagc agacgttttg gcagaaaacc aggttcttga tagcagtgtc 1200
cctaagagtc caagtcaaga tgttaaagca actgttagaa atttttcaga agccaagagt 1260
gagaaccqaa agaaaagctt tgaaaaaaca aaccctaaga ggaaaaaaga ttatcacaac 1320
tatcaaacgt tattcgaacc aagaacacac catccatata tcttggaat gcttctagct 1380
ccggacattc gacatgaaag aaatgtgatt ttgcagtggt ttcggtacat cattaaaaaa 1440
gacttttttg gactggatac taattctgcg aaaagtaaa atgtataggc atctggtgtt 1500
tcagcatata taactgaagc atgtgaaaca gtatcatcct cgttagtaga ggaaaacca 1560
aacccttttt tccgtcaaaa ttggatttgt aattaaattg taagcctcgt aggatgtatg 1620
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ttattttaat gtattgttct catgtaagaa tgactgatgt tgtgttagtt aagaattgaa 1800
gataggttta gcagtaaaga agaaagcttt taaaaggatt gattcagcta agcaaagttg 1860
ggcagagaaa tacagccatt ttgtttttta tgcagaaaag gaagatgttc tgtagcaagg 1920
gggaatatatt taaaaataaa ccagatcaaa ttaatacaat cagaagggtt cgaaatgtaa 1980
atattcctta tttaagacat gtttaaatte acctactagc acgacttaca tagctcaaat 2040
attgaatgtt taaaatatta atacagatgg ggccctctta tgtttagata aaattgaagt 2100
acttaattga agctttttta aaattgtaaa gttaaataaa gctattgaga tctttttgtc 2160
tctataata ccagggaatt tgagcttgtg ttctagtcac tgtactagct gtagctattg 2220
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gttgaagatt aacttttctt aacattgtga ttattgaagt tcatgaatct tgctgtcaag 2340
gaagaaaggt aagaaagctg atagctcctc catgttggtg aaatcctctc cagaatcttg 2400
gaacacctgg catgtgacc tagtgacgtc acagacctga gatgaagatt catgttttag 2460
cagtgttttc cagccttgta cccaccatac agatctgttt attctgtttc accctactcc 2520
tccagtgagc cccatatttt gggaaattat ctgccttata cattaactaa ttcaattcat 2580
gtaacactgt tgagtgttta ctctttgtac ctctattgtg cctatattaa aggtatacaa 2640
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tgattoccaa ccaactcagg atgaagtaac tagtgttaca actgagttga tattctaaaa 2760
tataaccocag tttgtacttt tattactagt tagcatacac attttatggc ttatgggtta 2820
ataaatgaat tcatggactc ctggactact ttcattgatg accatatctc cagggtgtt 2880
gttgatcccc acactgcctt aaggtatatt atagaaacag ttttattttt cattttttct 2940

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243

```

gtttcctgat aataaatgta tttaggactg aaaatactcc tgagtactcc cctggcctgta 3000
tgtctgacag tcttttagcta tgggtgactat tgtttatttt taatgggtat ttcagattcc 3060
aagtgtatgtt aaaattttcta aggagatata atatagcctg tatgggtttct actttatgga 3120
attatatgggt caatatattgt aaatatattcta tgagtttttgg gtgggtagag ggggtgctttg 3180
cctgtttttgg gtacagggttt ttttggattt agcttggttaa ttgttcaaac tttctgcctt 3240
ctacatttcct atcttattgt tcgtttaatc agtttctgaa atgtaagcat tacatgacta 3300
ttgggtgagtt gtgccttttta taactgaaat actttacttt ttctcatatc ctctataatt 3360
gacttctatt ttccttaatc aaaccagctc tgggaaattt aatacattta tattaattga 3420
gattattaata acatttggac tattaataaaa aaaaaaaaaa aaa 3463

```

<210> 225

<211> 495

<212> PRT

<213> Homo sapiens

<400> 225

```

Met Ala Glu Pro Thr Ser Asp Phe Glu Thr Pro Ile Gly Trp His Ala
1      5      10
Ser Pro Glu Leu Thr Pro Thr Leu Gly Pro Leu Ser Asp Thr Ala Pro
20     25     30
Pro Arg Asp Arg Trp Met Phe Trp Ala Met Leu Pro Pro Pro Pro Pro
35     40     45
Pro Leu Thr Ser Ser Leu Pro Ala Ala Gly Ser Lys Pro Ser Ser Glu
50     55     60
Ser Gln Pro Pro Met Glu Ala Gln Ser Leu Pro Gly Ala Pro Pro Pro
65     70     75     80
Phe Asp Ala Gln Ile Leu Pro Gly Ala Gln Pro Pro Phe Asp Ala Gln
85     90     95
Ser Pro Leu Asp Ser Gln Pro Gln Pro Ser Gly Gln Pro Trp Asn Phe
100    105    110
His Ala Ser Thr Ser Trp Tyr Trp Arg Gln Ser Ser Asp Arg Phe Pro
115    120    125
Arg His Gln Lys Ser Phe Asn Pro Ala Val Lys Asn Ser Tyr Tyr Pro
130    135    140
Arg Lys Tyr Asp Ala Lys Phe Thr Asp Phe Ser Leu Pro Pro Ser Arg
145    150    155    160
Lys Gln Lys Lys Lys Lys Arg Lys Glu Pro Val Phe His Phe Phe Cys
165    170    175
Asp Thr Cys Asp Arg Gly Phe Lys Asn Gln Glu Lys Tyr Asp Lys His
180    185    190
Met Ser Glu His Thr Lys Cys Pro Glu Leu Asp Cys Ser Phe Thr Ala
195    200    205
His Glu Lys Ile Val Gln Phe His Trp Arg Asn Met His Ala Pro Gly
210    215    220
Met Lys Lys Ile Lys Leu Asp Thr Pro Glu Glu Ile Ala Arg Trp Arg
225    230    235    240
Glu Glu Arg Arg Lys Asn Tyr Pro Thr Leu Ala Asn Ile Glu Arg Lys
245    250    255
Lys Lys Leu Lys Leu Glu Lys Glu Lys Arg Gly Ala Val Leu Thr Thr
260    265    270
Thr Gln Tyr Gly Lys Met Lys Gly Met Ser Arg His Ser Gln Met Ala
275    280    285
Lys Ile Arg Ser Pro Gly Lys Asn His Lys Trp Lys Asn Asp Asn Ser
290    295    300
Arg Gln Arg Ala Val Thr Gly Ser Gly Ser His Leu Cys Asp Leu Lys
305    310    315    320
Leu Glu Gly Pro Pro Glu Ala Asn Ala Asp Pro Leu Gly Val Leu Ile
325    330    335

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244

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Asn Ser Asp Ser Glu Ser Asp Lys Glu Glu Lys Pro Gln His Ser Val
      340                      345                      350
Ile Pro Lys Glu Val Thr Pro Ala Leu Cys Ser Leu Met Ser Ser Tyr
      355                      360                      365
Gly Ser Leu Ser Gly Ser Glu Ser Glu Pro Glu Glu Thr Pro Ile Lys
      370                      375                      380
Thr Glu Ala Asp Val Leu Ala Glu Asn Gln Val Leu Asp Ser Ser Ala
      385                      390                      395                      400
Pro Lys Ser Pro Ser Gln Asp Val Lys Ala Thr Val Arg Asn Phe Ser
      405                      410                      415
Glu Ala Lys Ser Glu Asn Arg Lys Lys Ser Phe Glu Lys Thr Asn Pro
      420                      425                      430
Lys Arg Lys Lys Asp Tyr His Asn Tyr Gln Thr Leu Phe Glu Pro Arg
      435                      440                      445
Thr His His Pro Tyr Leu Leu Glu Met Leu Leu Ala Pro Asp Ile Arg
      450                      455                      460
His Glu Arg Asn Val Ile Leu Gln Cys Val Arg Tyr Ile Ile Lys Lys
      465                      470                      475                      480
Asp Phe Phe Gly Leu Asp Thr Asn Ser Ala Lys Ser Lys Asp Val
      485                      490                      495

```

<210> 226
 <211> 942
 <212> DNA
 <213> Homo sapiens

```

<400> 226
atgagaattg cagtgatttg cttttgcttc ctaggcatca cctgtgccat accagttaaa 60
caggctgatt ctggaagttc tgaggaaaag cagctttaca acaaataccc agatgctgtg 120
gccacatggc taaaccctga cccatctcag aagcagaatc tcctagcccc acagaatgct 180
gtgtcctctg aagaaaccaa tgacttttaa caagagaccc ttccaagtaa gtccaacgaa 240
agccatgacc acatggatga tatggatgat gaagatgatg atgaccatgt ggacagccag 300
gactccattg actcgaacga ctctgatgat gtagatgaca ctgatgattc tcaccagtct 360
gatgagtctc accattctga tgaatctgat gaactgggtc ctgattttcc caccggacctg 420
ccagcaaccg aagttttcac tccagttgtc cccacagtag acacatatga tggccgaggt 480
gatagtgtgg tttatggact gaggtcaaaa tctaagaagt ttccgagacc tgacatccag 540
taccctgatg ctacagacga gcacatcacc tcacacatgg aaagcgagga gttgaatggt 600
gcatacaagg ccatccccgt tgcccaggac ctgaacgcgc cttctgattg ggacagccgt 660
gggaaggaca gttatgaaac gagtcagctg gatgaccaga gtgctgaagc ccacagccac 720
aagcagtcca gattatataa gcggaaagct aatgatgaga gcaatgagca ttccgatgtg 780
attgatagtc aggaactttc caaagtcagc cgtgaattcc acagccatga atttcacagc 840
catgaagata tgctggttgt agaccccaa agtaaggaag aagataaaca cctgaaattt 900
cgtattttctc atgaattaga tagtgcatct tctgaggtca at 942

```

<210> 227
 <211> 314
 <212> PRT
 <213> Homo sapiens

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<400> 227
Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
  1           5           10           15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
  20           25           30
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
  35           40           45
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu

```

245

50		55		60
Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu				
65		70		80
Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp Asp His				
	85		90	95
Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Val Asp				
	100		105	110
Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu				
	115		120	125
Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu				
	130		135	140
Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly				
	145		150	155
Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg				
	165		170	175
Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu His Ile Thr Ser His				
	180		185	190
Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala				
	195		200	205
Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser				
	210		215	220
Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Ala His Ser His				
	225		230	235
Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu				
	245		250	255
His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu				
	260		265	270
Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val Val Asp				
	275		280	285
Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile Ser His				
	290		295	300
Glu Leu Asp Ser Ala Ser Ser Glu Val Asn				
305		310		

<210> 228

<211> 1524

<212> DNA

<213> Homo sapiens

<400> 228

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gcagagcaca gcacgctcgg gaccagactc gtctcaggcc agttgcagcc ttctcagcca 60
aacgcgacc aaggaaaact cactaccatg agaattgcag tgatttgctt ttgcctccta 120
ggcatcacct gtgccatacc agttaaacag gctgattctg gaagttctga ggaaaagcag 180
ctttacaaca aatacccaga tgctgtggcc acatggctaa accctgaccc atctcagaag 240
cagaatctcc tagccccaca gacccttcca agtaagtcca acgaaagcca tgaccacatg 300
gatgatattg atgatgaaga tgatgatgac catgtggaca gccaggactc cattgactcg 360
aacgactctg atgatgtaga tgacactgat gattctcacc agtctgatga gtctcaccat 420
tctgatgaat ctgatgaact ggtcactgat tttccacagg acctgccagc aaccgaagtt 480
ttcactccag ttgtccccac agtagacaca tatgatggcc gaggtgatag tgtggtttat 540
ggactgaggt caaaatctaa gaagtttcgc agacctgaca tccagtaccc tgatgctaca 600
gacgaggaca tcacctcaca catggaaage gaggagttag atggtgcata caaggccatc 660
cccgttgccc aggacctgaa cgcgccttct gattgggaca gccgtgggaa ggacagttat 720
gaaacgagtc agctggatga ccagagtgct gaaaccacaa gccacaagca gtccagatta 780
tataagcgga aagccaatga tgagagcaat gagcattccg atgtgattga tagtcaggaa 840
ctttccaaag tcagccgtga attccacagc catgaatttc acagccatga agatattgctg 900
gtttagtagc ccaaaagtaa ggaagaagat aaacacctga aatttcgtat ttctcatgaa 960
ttagatagtg catcttctga ggtcaattaa aaggagaaaa aatacaattt ctcactttgc 1020

```

246

```

atttagtcaa aagaaaaaat gctttatagc aaaatgaaag agaacatgaa atgcttcttt 1080
ctcagtttat tgggttgaaat tgtatctatt tgagtctgga aataactaat gtgtttgata 1140
attagtttag tttgtggctt catggaaact ccctgtaaac taaaagcttc agggttatgt 1200
ctatgttcat tctatagaag aaatgcaaac tatcactgta ttttaataatt tgttattctc 1260
tcatgaatag aaatttatgt agaagcaaac aaaatacttt taccactta aaaagagaat 1320
ataacatttt atgtcactat aatcttttgt tttttaagtt agtgtatatt ttgttgtgat 1380
tatctttttg tgggtgtgaat aaatctttta tcttgaatgt aataagaatt tgggtggtgtc 1440
aattgcttat ttgttttccc acggttgtcc agcaattaat aaaacataac cttttttact 1500
gcctaaaaaa aaaaaaaaaa aaaa                                     1524

```

<210> 229

<211> 300

<212> PRT

<213> Homo sapiens

<400> 229

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Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
1      5      10
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
20     25     30
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
35     40     45
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser
50     55     60
Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp
65     70     75     80
Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp
85     90     95
Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser
100    105    110
Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala
115    120    125
Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly
130    135    140
Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe
145    150    155    160
Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr
165    170    175
Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro
180    185    190
Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys
195    200    205
Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His
210    215    220
Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser
225    230    235    240
Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser
245    250    255
Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val
260    265    270
Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile
275    280    285
Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
290    295    300

```

<210> 230

<211> 861

<212> DNA

<213> Homo sapiens

<400> 230

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atgagaattg cagtgatttg cttttgcctc ctaggcatca cctgtgccat accagttaaa 60
caggctgatt ctggaagttc tgaggaaaag cagaatgctg tgtcctctga agaaaccaat 120
gacttttaac aagagaccct tccaagtaag tccaacgaaa gccatgacca catggatgat 180
atggatgatg aagatgatga tgaccatgtg gacagccagg actccattga ctogaacgac 240
tctgatgatg tagatgacac tgatgattct caccagtctg atgagtctca ccattctgat 300
gaatctgatg aactggtcac tgattttccc acggacctgc cagcaaccga agttttcact 360
ccagttgtcc ccacagtaga cacatatgat ggccgaggtg atagtgtggt ttatggactg 420
aggtcaaaat ctaagaagtt tgcagacct gacatccagt accctgatgc tacagacgag 480
cacatcacct cacacatgga aagcgaggag ttgaatggtg catacaaggc catccccgtt 540
gccaggacc tgaacgcgcc ttctgattgg gacagccgtg ggaaggacag ttatgaaacg 600
agtcagctgg atgaccagag tgcagaagcc cacagccaca agcagtcag attatataag 660
cggaaagcta atgatgagag caatgagcat tccgatgtga ttgatagtca ggaactttcc 720
aaagtcagcc gtgaattcca cagccatgaa ttccacagcc atgaagatat gctggttgta 780
gaccccaaaa gtaaggaaga agataaacac ctgaaatttc gtatttctca tgaattagat 840
agtgcattct ctgaggtcaa t                                     861

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<210> 231

<211> 287

<212> PRT

<213> Homo sapiens

<400> 231

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Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
 1           5           10          15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Asn
          20          25          30
Ala Val Ser Ser Glu Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro
          35          40          45
Ser Lys Ser Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu
          50          55          60
Asp Asp Asp Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp
          65          70          75          80
Ser Asp Asp Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser
          85          90          95
His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp
          100         105         110
Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr
          115         120         125
Tyr Asp Gly Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser
          130         135         140
Lys Lys Phe Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu
          145         150         155         160
His Ile Thr Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys
          165         170         175
Ala Ile Pro Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser
          180         185         190
Arg Gly Lys Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala
          195         200         205
Glu Ala His Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn
          210         215         220
Asp Glu Ser Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser
          225         230         235         240
Lys Val Ser Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp
          245         250         255

```

248

Met Leu Val Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys
 260 265 270
 Phe Arg Ile Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
 275 280 285

<210> 232
 <211> 838
 <212> DNA
 <213> Homo sapiens

<400> 232
 ctcagagcca cccacagccg cagccatgct gtgcctcctg ctcaccctgg gcgtggccct 60
 ggtctgtggt gtcccgccca tggacatccc ccagaccaag caggacctgg agctcccaaa 120
 gttggcaggg acctggcact ccatggccat ggcgaccaac aacatctccc tcatggcgac 180
 actgaaggcc cctctgaggg tccacatcac ctcactgttg cccacccccg aggacaacct 240
 ggagatcggt ctgcacagat gggagaacaa cagctgtggt gagaagaagg tccttggaga 300
 gaagactgag aatccaaaga agttcaagat caactatacg gtggcgaacg aggccacgct 360
 gctcgatact gactacgaca atttcctggt tctctgccta caggacacca ccacccccat 420
 ccagagcatg atgtgccagt acctggccag agtcctggtg gaggacgatg agatcatgca 480
 gggattcatc agggctttca ggccccctgcc caggcaccta tggacttgc tggacttgaa 540
 acagatggaa gagccgtgcc gtttctaggt gagctcctgc ctggtcctgc ctctggctc 600
 acctccgcct ccaggaagac cagactccca cccttcaca cctccagagc agtgggactt 660
 cctcctgccc tttcaaagaa taaccacagc tcagaagacg atgacgtggt catctgtgtc 720
 gccatcccct tctgtctgca cacctgcacc acggccatgg ggaggctgct ccctgggggc 780
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<210> 233
 <211> 180
 <212> PRT
 <213> Homo sapiens

<400> 233
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 20 25 30
 Leu Ala Gly Thr Trp His Ser Met Ala Met Ala Thr Asn Asn Ile Ser
 35 40 45
 Leu Met Ala Thr Leu Lys Ala Pro Leu Arg Val His Ile Thr Ser Leu
 50 55 60
 Leu Pro Thr Pro Glu Asp Asn Leu Glu Ile Val Leu His Arg Trp Glu
 65 70 75 80
 Asn Asn Ser Cys Val Glu Lys Lys Val Leu Gly Glu Lys Thr Glu Asn
 85 90 95
 Pro Lys Lys Phe Lys Ile Asn Tyr Thr Val Ala Asn Glu Ala Thr Leu
 100 105 110
 Leu Asp Thr Asp Tyr Asp Asn Phe Leu Phe Leu Cys Leu Gln Asp Thr
 115 120 125
 Thr Thr Pro Ile Gln Ser Met Met Cys Gln Tyr Leu Ala Arg Val Leu
 130 135 140
 Val Glu Asp Asp Glu Ile Met Gln Gly Phe Ile Arg Ala Phe Arg Pro
 145 150 155 160
 Leu Pro Arg His Leu Trp Tyr Leu Leu Asp Leu Lys Gln Met Glu Glu
 165 170 175
 Pro Cys Arg Phe
 180

<210> 234
 <211> 851
 <212> DNA
 <213> Homo sapiens

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 agtcccaaa gttggcaggg acctggcact ccatggccat ggcgaccaac aacatctccc 180
 tcatggcgac actgaaggcc cctctgaggg tccacatcac ctactgttg cccacccccg 240
 aggacaacct ggagatcggt ctgcacagat gggagaacaa cagctgtggt gagaagaagg 300
 tccttgagaga gaagactgag aatccaaaga agttcaagat caactatacg gtggcgaacg 360
 aggccacgct gctcgatact gactacgaca atttcctggt tctctgccta caggacacca 420
 ccacccccat ccagagcatg atgtgccagt acctggccag agtcctgggt gaggacgatg 480
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 ctctgggtg acctgtaaac ccaacagctc acctccgct ccaggaagac cagactccca 660
 cccttcaca cctccagagc agtgggactt cctcctgccc tttcaaagaa taaccacagc 720
 tcagaagacg atgacgtggt catctgtgtc gccatcccc tctgtgtgca cactgcacc 780
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 cttggagcat g 851

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 <211> 811
 <212> DNA
 <213> Homo sapiens

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 aggacctgga gctcccaaag ttggcagggc cctggcactc catggccatg gcgaccaaca 180
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 tggcgaacga ggccacgctg ctcgatactg actacgacaa tttcctgttt ctctgcctac 420
 aggacaccac cacccccatac cagagcatga tgtgccagta cctggccaga gtcctgggtg 480
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<210> 236
 <211> 850
 <212> DNA
 <213> Homo sapiens

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 aggacctgga gctcccaaag ttggcagggc cctggcactc catggccatg gcgaccaaca 180
 acatctccct catggcgaca ctgaaggccc ctctgagggg ccacatcacc tctactgttg 240
 ccacccccga ggacaacctg gagatcggtc tgcacagatg ggagaacaac agctgtgttg 300
 agaagaaggt ccttgagagag aagactgrga atccaaagaa gttcaagatc aactatacgg 360
 tggcgaacga ggccacgctg ctcgatactg actacgacaa tttcctgttt ctctgcctac 420
 aggacaccac cacccccatac cagagcatga tgtgccagta cctggccaga gtcctgggtg 480

250

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aggacgatga gatcatgcag ggattcatca gggcttttcag gcccctgccc aggcacctat 540
ggctacttgct ggacttgaaa cagatggaag agccgtgccg tttctagtga cctgtaaacc 600
caacagctca cctccgcctc caggaagacc agactccac ccttccacac ctccagagca 660
gtgggacttc ctccctgccct ttcaaagaat aaccacagct cagaagacga tgacgtggtc 720
atctgtgtcg ccatccccctt cctgctgcac acctgcacca cggccatggg gaggctgctc 780
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<210> 237

<211> 598

<212> DNA

<213> Homo sapiens

<400> 237

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aggacctgga gctcccaaag gacaccacca ccccatcca gagcatgatg tgccagtacc 180
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cctgcccttt caaagaataa ccacagctca gaagacgatg acgtgggtcat ctgtgtcgcc 480
atcccttcc tgcctgcacac ctgcaccacg gccatgggga ggctgctccc tgggggcaga 540
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<210> 238

<211> 86

<212> PRT

<213> Homo sapiens

<400> 238

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      20             25             30
Asp Thr Thr Thr Pro Ile Gln Ser Met Met Cys Gln Tyr Leu Ala Arg
      35             40             45
Val Leu Val Glu Asp Asp Glu Ile Met Gln Gly Phe Ile Arg Ala Phe
      50             55             60
Arg Pro Leu Pro Arg His Leu Trp Tyr Leu Leu Asp Leu Lys Gln Met
      65             70             75             80
Glu Glu Pro Cys Arg Phe
                        85

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<210> 239

<211> 814

<212> DNA

<213> Homo sapiens

<400> 239

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aggacctgga gacactgaag gcccctctga gggctccacat cactcactg ttgccaccc 180
ccgaggacaa cctggagatc gttctgcaca gatgggagaa caacagctgt gttgagaaga 240
aggtccttgg agagaagact grgaatccaa agaagttcaa gatcaactat acggtggcga 300
acgaggccac gctgctcgat actgactacg acaatttctt gtttctctgc ctacaggaca 360
ccaccacccc catccagagc atgatgtgcc agtacctggc cagagtcctg gtggaggacg 420

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251

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agctcagaag acgatgacgt ggtcatctgt gtcgccatcc ccttcctgct gcacacctgc 720
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acccttggag catgaaaaaa aaaaaaaaaa aaaa 814

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<210> 240
 <211> 158
 <212> PRT
 <213> Homo sapiens

<400> 240

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Pro	Ala	Met	Asp	Ile	Pro	Gln	Thr	Lys	Gln	Asp	Leu	Glu	Leu	Pro	Lys
			20					25					30		
Ala	Pro	Leu	Arg	Val	His	Ile	Thr	Ser	Leu	Leu	Pro	Thr	Pro	Glu	Asp
			35				40					45			
Asn	Leu	Glu	Ile	Val	Leu	His	Arg	Trp	Glu	Asn	Asn	Ser	Cys	Val	Glu
			50			55					60				
Lys	Lys	Val	Leu	Gly	Glu	Lys	Thr	Glu	Asn	Pro	Lys	Lys	Phe	Lys	Ile
65					70				75						80
Asn	Tyr	Thr	Val	Ala	Asn	Glu	Ala	Thr	Leu	Leu	Asp	Thr	Asp	Tyr	Asp
			85					90					95		
Asn	Phe	Leu	Phe	Leu	Cys	Leu	Gln	Asp	Thr	Thr	Thr	Pro	Ile	Gln	Ser
			100					105					110		
Met	Met	Cys	Gln	Tyr	Leu	Ala	Arg	Val	Leu	Val	Glu	Asp	Asp	Glu	Ile
			115				120					125			
Met	Gln	Gly	Phe	Ile	Arg	Ala	Phe	Arg	Pro	Leu	Pro	Arg	His	Leu	Trp
			130			135					140				
Tyr	Leu	Leu	Asp	Leu	Lys	Gln	Met	Glu	Glu	Pro	Cys	Arg	Phe		
145					150					155					

<210> 241
 <211> 158
 <212> PRT
 <213> Homo sapiens

<400> 241

Met	Leu	Cys	Leu	Leu	Leu	Thr	Leu	Gly	Val	Ala	Leu	Val	Cys	Gly	Val
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Pro	Ala	Met	Asp	Ile	Pro	Gln	Thr	Lys	Gln	Asp	Leu	Glu	Thr	Leu	Lys
			20					25					30		
Ala	Pro	Leu	Arg	Val	His	Ile	Thr	Ser	Leu	Leu	Pro	Thr	Pro	Glu	Asp
			35				40					45			
Asn	Leu	Glu	Ile	Val	Leu	His	Arg	Trp	Glu	Asn	Asn	Ser	Cys	Val	Glu
			50			55					60				
Lys	Lys	Val	Leu	Gly	Glu	Lys	Thr	Glu	Asn	Pro	Lys	Lys	Phe	Lys	Ile
65					70				75						80
Asn	Tyr	Thr	Val	Ala	Asn	Glu	Ala	Thr	Leu	Leu	Asp	Thr	Asp	Tyr	Asp
			85					90					95		
Asn	Phe	Leu	Phe	Leu	Cys	Leu	Gln	Asp	Thr	Thr	Thr	Pro	Ile	Gln	Ser
			100					105					110		
Met	Met	Cys	Gln	Tyr	Leu	Ala	Arg	Val	Leu	Val	Glu	Asp	Asp	Glu	Ile
			115				120					125			

Met Gln Gly Phe Ile Arg Ala Phe Arg Pro Leu Pro Arg His Leu Trp
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 Tyr Leu Leu Asp Leu Lys Gln Met Glu Glu Pro Cys Arg Phe
 145 150 155

<210> 242
 <211> 2707
 <212> DNA
 <213> Homo sapiens

<400> 242
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 catcagatct ggccatggag ggctgaacca gctgggaggg gcctttgtga atggcagacc 240
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 cagctgcgtg gccaccaagt cctcagatcc cggacacacg ctgatcccca gctcagctgt 660
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<210> 243
 <211> 450
 <212> PRT
 <213> Homo sapiens

<400> 243

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          20           25           30
Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser
          35           40           45
Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
          50           55           60
Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
65          70          75          80
Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
          85          90          95
Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu
          100         105         110
Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile
          115         120         125
Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met
          130         135         140
Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile
145         150         155         160
Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu
          165         170         175
Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly
          180         185         190
Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu
          195         200         205
Ser Ile Asp Ser Gln Ser Ser Ser Ser Gly Pro Arg Lys His Leu Arg
          210         215         220
Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe
225         230         235         240
Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys
          245         250         255
Gly Glu Gln Gly Leu Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp
          260         265         270
Asp Gly Lys Ala Thr Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn
          275         280         285
Leu Ser Thr His Gln Thr Tyr Pro Val Val Ala Asp Pro His Ser Pro
          290         295         300
Phe Ala Ile Lys Gln Glu Thr Pro Glu Val Ser Ser Ser Ser Ser Thr
305         310         315         320
Pro Ser Ser Leu Ser Ser Ser Ala Phe Leu Asp Leu Gln Gln Val Gly
          325         330         335
Ser Gly Val Pro Pro Phe Asn Ala Phe Pro His Ala Ala Ser Val Tyr
          340         345         350
Gly Gln Phe Thr Gly Gln Ala Leu Leu Ser Gly Arg Glu Met Val Gly
          355         360         365
Pro Thr Leu Pro Gly Tyr Pro Pro His Ile Pro Thr Ser Gly Gln Gly
          370         375         380
Ser Tyr Ala Ser Ser Ala Ile Ala Gly Met Val Ala Gly Ser Glu Tyr
385         390         395         400
Ser Gly Asn Ala Tyr Gly His Thr Pro Tyr Ser Ser Tyr Ser Glu Ala

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254

			405					410				415			
Trp	Arg	Phe	Pro	Asn	Ser	Ser	Leu	Leu	Ser	Ser	Pro	Tyr	Tyr	Tyr	Ser
			420					425				430			
Ser	Thr	Ser	Arg	Pro	Ser	Ala	Pro	Pro	Thr	Thr	Ala	Thr	Ala	Phe	Asp
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His	Leu														
	450														

<210> 244
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 <212> DNA
 <213> Homo sapiens

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<400> 244
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 ccaggctgtc agctgacctc tttttcctgc tgctgtgaag gtatagcacc ancccaggtc 1860
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 cccnntgaa gccagcgata gangggtccc tctctgntc ccagcagct cctgccccca 2160
 naggcctgac tgtatatact gtaaataaaa ctttgtttgg gtcaagcttc cttctttcta 2220
 acccccnaga ctttggcctc tgagtgaat gtctctcttt gccctgtggg gcttctctcc 2280

255

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<210> 245
 <211> 387
 <212> PRT
 <213> Homo sapiens

<400> 245
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 20 25 30
 Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser
 35 40 45
 Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
 50 55 60
 Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
 65 70 75 80
 Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
 85 90 95
 Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu
 100 105 110
 Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile
 115 120 125
 Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met
 130 135 140
 Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile
 145 150 155 160
 Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu
 165 170 175
 Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly
 180 185 190
 Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu
 195 200 205
 Ser Ile Asp Ser Gln Ser Ser Ser Gly Pro Arg Lys His Leu Arg
 210 215 220
 Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe
 225 230 235 240
 Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys
 245 250 255
 Gly Glu Gln Gly Leu Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp
 260 265 270
 Asp Gly Lys Ala Thr Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn
 275 280 285
 Leu Ser Thr His Gln Thr Tyr Pro Val Val Ala Gly Arg Glu Met Val
 290 295 300
 Gly Pro Thr Leu Pro Gly Tyr Pro Pro His Ile Pro Thr Ser Gly Gln
 305 310 315 320
 Gly Ser Tyr Ala Ser Ser Ala Ile Ala Gly Met Val Ala Gly Ser Glu
 325 330 335
 Tyr Ser Gly Asn Ala Tyr Gly His Thr Pro Tyr Ser Ser Tyr Ser Glu
 340 345 350
 Ala Trp Arg Phe Pro Asn Ser Ser Leu Leu Ser Ser Pro Tyr Tyr Tyr
 355 360 365
 Ser Ser Thr Ser Arg Pro Ser Ala Pro Pro Thr Thr Ala Thr Ala Phe
 370 375 380
 Asp His Leu

385

<210> 246
 <211> 387
 <212> PRT
 <213> Homo sapiens

<400> 246
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 20 25 30
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 35 40 45
 Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
 50 55 60
 Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
 65 70 75 80
 Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
 85 90 95
 Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu
 100 105 110
 Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile
 115 120 125
 Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met
 130 135 140
 Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile
 145 150 155 160
 Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu
 165 170 175
 Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly
 180 185 190
 Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu
 195 200 205
 Ser Ile Asp Ser Gln Ser Ser Ser Gly Pro Arg Lys His Leu Arg
 210 215 220
 Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe
 225 230 235 240
 Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys
 245 250 255
 Gly Glu Gln Gly Leu Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp
 260 265 270
 Asp Gly Lys Ala Thr Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn
 275 280 285
 Leu Ser Thr His Gln Thr Tyr Pro Val Val Ala Gly Arg Glu Met Val
 290 295 300
 Gly Pro Thr Leu Pro Gly Tyr Pro Pro His Ile Pro Thr Ser Gly Gln
 305 310 315 320
 Gly Ser Tyr Ala Ser Ser Ala Ile Ala Gly Met Val Ala Gly Ser Glu
 325 330 335
 Tyr Ser Gly Asn Ala Tyr Gly His Thr Pro Tyr Ser Ser Tyr Ser Glu
 340 345 350
 Ala Trp Gly Phe Pro Asn Ser Ser Leu Leu Ser Ser Pro Tyr Tyr Tyr
 355 360 365
 Ser Ser Thr Ser Arg Pro Ser Ala Pro Pro Thr Thr Ala Thr Ala Phe
 370 375 380
 Asp His Leu

385

<210> 247
<211> 2641
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(2641)
<223> n = A,T,C or G

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ctctcgccag ctccgcgtca gccatggctg cgctcagcaag atccttggca ggtactacga 360
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gccctgtggg gcttctctcc ttgatgcttc tttctttttt taaagacaac ctgccattac 2580
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a

2641

<210> 248
 <211> 398
 <212> PRT
 <213> Homo sapiens

<400> 248
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 20 25 30
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 35 40 45
 Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
 50 55 60
 Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
 65 70 75 80
 Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
 85 90 95
 Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu
 100 105 110
 Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile
 115 120 125
 Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met
 130 135 140
 Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile
 145 150 155 160
 Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu
 165 170 175
 Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly
 180 185 190
 Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu
 195 200 205
 Ser Ile Asp Ser Gln Ser Ser Ser Gly Pro Arg Lys His Leu Arg
 210 215 220
 Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe
 225 230 235 240
 Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys
 245 250 255
 Gly Glu Gln Gly Leu Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp
 260 265 270
 Asp Gly Lys Ala Thr Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn
 275 280 285
 Leu Ser Thr His Gln Thr Tyr Pro Val Val Ala Ala Pro Pro Phe Trp
 290 295 300
 Ile Cys Ser Lys Ser Ala Pro Gly Ser Arg Pro Ser Met Pro Phe Pro
 305 310 315 320
 Met Leu Pro Pro Cys Thr Gly Ser Ser Arg Ala Arg Pro Ser Ser Gln
 325 330 335
 Gly Glu Arg Trp Trp Gly Pro Arg Cys Pro Asp Thr His Pro Thr Ser
 340 345 350
 Pro Pro Ala Asp Arg Ala Ala Met Pro Pro Leu Pro Ser Gln Ala Trp
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 370 375 380
 Pro Pro Thr Ala Arg Pro Gly Ala Ser Pro Thr Pro Ala Cys
 385 390 395

<210> 249
 <211> 2410
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(2410)
 <223> n = A,T,C or G

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 aaaaaaaaaa 2410

<210> 250
 <211> 321
 <212> PRT

260

<213> Homo sapiens

<400> 250

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          20           25           30
Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser
          35           40           45
Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
          50           55           60
Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
65          70          75          80
Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
          85          90          95
Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu
          100         105         110
Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile
          115         120         125
Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met
          130         135         140
Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile
145          150          155          160
Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu
          165         170         175
Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly
          180         185         190
Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu
          195         200         205
Ser Ile Asp Ser Gln Ser Ser Ser Gly Pro Arg Lys His Leu Arg
          210         215         220
Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe
225          230          235          240
Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys
          245         250         255
Gly Glu Gln Gly Glu Arg Trp Trp Gly Pro Arg Cys Pro Asp Thr His
          260         265         270
Pro Thr Ser Pro Pro Ala Asp Arg Ala Ala Met Pro Pro Leu Pro Ser
          275         280         285
Gln Ala Trp Trp Gln Glu Val Asn Thr Leu Ala Met Pro Met Ala Thr
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Pro Pro Thr Pro Pro Thr Ala Arg Pro Gly Ala Ser Pro Thr Pro Ala
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Cys

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<210> 251

<211> 2308

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(2308)

<223> n = A,T,C or G

<400> 251

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<210> 252

<211> 287

<212> PRT

<213> Homo sapiens

<400> 252

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20           25           30
Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser
35           40           45
Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
50           55           60
Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
65           70           75           80
Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
85           90           95

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Arg	Gln	Asn	Pro	Thr	Met	Phe	Ala	Trp	Glu	Ile	Arg	Asp	Arg	Leu	Leu
		100						105					110		
Ala	Glu	Gly	Val	Cys	Asp	Asn	Asp	Thr	Val	Pro	Ser	Val	Ser	Ser	Ile
		115					120					125			
Asn	Arg	Ile	Ile	Arg	Thr	Lys	Val	Gln	Gln	Pro	Phe	Asn	Leu	Pro	Met
	130					135					140				
Asp	Ser	Cys	Val	Ala	Thr	Lys	Ser	Leu	Ser	Pro	Gly	His	Thr	Leu	Ile
145					150					155				160	
Pro	Ser	Ser	Ala	Val	Thr	Pro	Pro	Glu	Ser	Pro	Gln	Ser	Asp	Ser	Leu
			165					170						175	
Gly	Ser	Thr	Tyr	Ser	Ile	Asn	Gly	Leu	Leu	Gly	Ile	Ala	Gln	Pro	Gly
		180						185					190		
Ser	Asp	Lys	Arg	Lys	Met	Asp	Asp	Ser	Asp	Gln	Asp	Ser	Cys	Arg	Leu
	195						200				205				
Ser	Ile	Asp	Ser	Gln	Ser	Ser	Ser	Ser	Gly	Pro	Arg	Lys	His	Leu	Arg
	210					215					220				
Thr	Asp	Ala	Phe	Ser	Gln	His	His	Leu	Glu	Pro	Leu	Glu	Cys	Pro	Phe
225					230					235				240	
Glu	Arg	Gln	His	Tyr	Pro	Glu	Ala	Tyr	Ala	Ser	Pro	Ser	His	Thr	Lys
			245					250						255	
Gly	Glu	Gln	Glu	Val	Asn	Thr	Leu	Ala	Met	Pro	Met	Ala	Thr	Pro	Pro
		260						265					270		
Thr	Pro	Pro	Thr	Ala	Arg	Pro	Gly	Ala	Ser	Pro	Thr	Pro	Ala	Cys	
		275					280						285		

<210> 253

<211> 2148

<212> DNA

<213> Homo sapiens

<400> 253

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<210> 254

<211> 509

<212> PRT

<213> Homo sapiens

<400> 254

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Ser Leu Leu Lys Asp Glu Ala Leu Ala Ile Ala Ala Leu Glu Leu Leu
35     40     45
Pro Arg Glu Leu Phe Pro Pro Leu Phe Met Ala Ala Phe Asp Gly Arg
50     55     60
His Ser Gln Thr Leu Lys Ala Met Val Gln Ala Trp Pro Phe Thr Cys
65     70     75     80
Leu Pro Leu Gly Val Leu Met Lys Gly Gln His Leu His Leu Glu Thr
85     90     95
Phe Lys Ala Val Leu Asp Gly Leu Asp Val Leu Leu Ala Gln Glu Val
100    105    110
Arg Pro Arg Arg Trp Lys Leu Gln Val Leu Asp Leu Arg Lys Asn Ser
115    120    125
His Gln Asp Phe Trp Thr Val Trp Ser Gly Asn Arg Ala Ser Leu Tyr
130    135    140
Ser Phe Pro Glu Pro Glu Ala Ala Gln Pro Met Thr Lys Lys Arg Lys
145    150    155    160
Val Asp Gly Leu Ser Thr Glu Ala Glu Gln Pro Phe Ile Pro Val Glu
165    170    175
Val Leu Val Asp Leu Phe Leu Lys Glu Gly Ala Cys Asp Glu Leu Phe
180    185    190
Ser Tyr Leu Ile Glu Lys Val Lys Arg Lys Lys Asn Val Leu Arg Leu
195    200    205
Cys Cys Lys Lys Leu Lys Ile Phe Ala Met Pro Met Gln Asp Ile Lys
210    215    220
Met Ile Leu Lys Met Val Gln Leu Asp Ser Ile Glu Asp Leu Glu Val
225    230    235    240
Thr Cys Thr Trp Lys Leu Pro Thr Leu Ala Lys Phe Ser Pro Tyr Leu
245    250    255
Gly Gln Met Ile Asn Leu Arg Arg Leu Leu Leu Ser His Ile His Ala
260    265    270
Ser Ser Tyr Ile Ser Pro Glu Lys Glu Glu Gln Tyr Ile Ala Gln Phe
275    280    285
Thr Ser Gln Phe Leu Ser Leu Gln Cys Leu Gln Ala Leu Tyr Val Asp
290    295    300
Ser Leu Phe Phe Leu Arg Gly Arg Leu Asp Gln Leu Leu Arg His Val
305    310    315    320
Met Asn Pro Leu Glu Thr Leu Ser Ile Thr Asn Cys Arg Leu Ser Glu

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264

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Gly	Asp	Val	Met	His	Leu	Ser	Gln	Ser	Pro	Ser	Val	Ser	Gln	Leu	Ser	
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Val	Leu	Ser	Leu	Ser	Gly	Val	Met	Leu	Thr	Asp	Val	Ser	Pro	Glu	Pro	
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Leu	Gln	Ala	Leu	Leu	Glu	Arg	Ala	Ser	Ala	Thr	Leu	Gln	Asp	Leu	Val	
	370					375					380					
Phe	Asp	Glu	Cys	Gly	Ile	Thr	Asp	Asp	Gln	Leu	Leu	Ala	Leu	Leu	Pro	
385					390					395					400	
Ser	Leu	Ser	His	Cys	Ser	Gln	Leu	Thr	Thr	Leu	Ser	Phe	Tyr	Gly	Asn	
			405						410					415		
Ser	Ile	Ser	Ile	Ser	Ala	Leu	Gln	Ser	Leu	Leu	Gln	His	Leu	Ile	Gly	
			420					425					430			
Leu	Ser	Asn	Leu	Thr	His	Val	Leu	Tyr	Pro	Val	Pro	Leu	Glu	Ser	Tyr	
		435					440					445				
Glu	Asp	Ile	His	Gly	Thr	Leu	His	Leu	Glu	Arg	Leu	Ala	Tyr	Leu	His	
	450					455					460					
Ala	Arg	Leu	Arg	Glu	Leu	Leu	Cys	Glu	Leu	Gly	Arg	Pro	Ser	Met	Val	
465				470						475					480	
Trp	Leu	Ser	Ala	Asn	Pro	Cys	Pro	His	Cys	Gly	Asp	Arg	Thr	Phe	Tyr	
			485						490					495		
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			500					505								

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<210> 255
<211> 2261
<212> DNA
<213> Homo sapiens
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265

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<210> 256

<211> 587

<212> PRT

<213> Homo sapiens

<400> 256

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Val Arg Val Lys Ala Tyr Tyr Arg Gly Asp Ile Met Ile Thr His Phe
20          25          30
Glu Pro Ser Ile Ser Phe Glu Gly Leu Cys Asn Glu Val Arg Asp Met
35          40          45
Cys Ser Phe Asp Asn Glu Gln Leu Phe Thr Met Lys Trp Ile Asp Glu
50          55          60
Glu Gly Asp Pro Cys Thr Val Ser Ser Gln Leu Glu Leu Glu Glu Ala
65          70          75          80
Phe Arg Leu Tyr Glu Leu Asn Lys Asp Ser Glu Leu Leu Ile His Val
85          90          95
Phe Pro Cys Val Pro Glu Arg Pro Gly Met Pro Cys Pro Gly Glu Asp
100          105          110
Lys Ser Ile Tyr Arg Arg Gly Ala Arg Arg Trp Arg Lys Leu Tyr Cys
115          120          125
Ala Asn Gly His Thr Phe Gln Ala Lys Arg Phe Asn Arg Arg Ala His
130          135          140
Cys Ala Ile Cys Thr Asp Arg Ile Trp Gly Leu Gly Arg Gln Gly Tyr
145          150          155          160
Lys Cys Ile Asn Cys Lys Leu Leu Val His Lys Lys Cys His Lys Leu
165          170          175
Val Thr Ile Glu Cys Gly Arg His Ser Leu Pro Gln Glu Pro Val Met
180          185          190
Pro Met Asp Gln Ser Ser Met His Ser Asp His Ala Gln Thr Val Ile
195          200          205
Pro Tyr Asn Pro Ser Ser His Glu Ser Leu Asp Gln Val Gly Glu Glu
210          215          220
Lys Glu Ala Met Asn Thr Arg Glu Ser Gly Lys Ala Ser Ser Ser Leu
225          230          235          240
Gly Leu Gln Asp Phe Asp Leu Leu Arg Val Ile Gly Arg Gly Ser Tyr
245          250          255
Ala Lys Val Leu Leu Val Arg Leu Lys Lys Thr Asp Arg Ile Tyr Ala
260          265          270
Met Lys Val Val Lys Lys Glu Leu Val Asn Asp Asp Glu Asp Ile Asp
275          280          285
Trp Val Gln Thr Glu Lys His Val Phe Glu Gln Ala Ser Asn His Pro
290          295          300
Phe Leu Val Gly Leu His Ser Cys Phe Gln Thr Glu Ser Arg Leu Phe
305          310          315          320

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 355 360 365
 Asp Leu Lys Leu Asp Asn Val Leu Leu Asp Ser Glu Gly His Ile Lys
 370 375 380
 Leu Thr Asp Tyr Gly Met Cys Lys Glu Gly Leu Arg Pro Gly Asp Thr
 385 390 395 400
 Thr Ser Thr Phe Cys Gly Thr Pro Asn Tyr Ile Ala Pro Glu Ile Leu
 405 410 415
 Arg Gly Glu Asp Tyr Gly Phe Ser Val Asp Trp Trp Ala Leu Gly Val
 420 425 430
 Leu Met Phe Glu Met Met Ala Gly Arg Ser Pro Phe Asp Ile Val Gly
 435 440 445
 Ser Ser Asp Asn Pro Asp Gln Asn Thr Glu Asp Tyr Leu Phe Gln Val
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 Ile Leu Glu Lys Gln Ile Arg Ile Pro Arg Ser Leu Ser Val Lys Ala
 465 470 475 480
 Ala Ser Val Leu Lys Ser Phe Leu Asn Lys Asp Pro Lys Glu Arg Leu
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 Gly Cys His Pro Gln Thr Gly Phe Ala Asp Ile Gln Gly His Pro Phe
 500 505 510
 Phe Arg Asn Val Asp Trp Asp Met Met Glu Gln Lys Gln Val Val Pro
 515 520 525
 Pro Phe Lys Pro Asn Ile Ser Gly Glu Phe Gly Leu Asp Asn Phe Asp
 530 535 540
 Ser Gln Phe Thr Asn Glu Pro Val Gln Leu Thr Pro Asp Asp Asp Asp
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<210> 257

<211> 6742

<212> DNA

<213> Homo sapiens

<400> 257

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<211> 1834

<212> DNA

<213> Homo sapiens

<400> 261

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275

<210> 262
 <211> 343
 <212> PRT
 <213> Homo sapiens

<400> 262

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Lys Val Ser Thr Leu Lys Asp Ile Ile Pro His Pro Ser Tyr Leu Gln
      115          120          125
Glu Gly Ser Gln Gly Asp Ile Ala Leu Leu Gln Leu Ser Arg Pro Ile
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Thr Phe Ser Arg Tyr Ile Arg Pro Ile Cys Leu Pro Ala Ala Asn Ala
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Ser Phe Pro Asn Gly Leu His Cys Thr Val Thr Gly Trp Gly His Val
      165          170          175
Ala Pro Ser Val Ser Leu Leu Thr Pro Lys Pro Leu Gln Gln Leu Glu
      180          185          190
Val Pro Leu Ile Ser Arg Glu Thr Cys Asn Cys Leu Tyr Asn Ile Asp
      195          200          205
Ala Lys Pro Glu Glu Pro His Phe Val Gln Glu Asp Met Val Cys Ala
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Gly Tyr Val Glu Gly Gly Lys Asp Ala Cys Gln Gly Asp Ser Gly Gly
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Ser Trp Gly Asp Ala Cys Gly Ala Arg Asn Arg Pro Gly Val Tyr Thr
      260          265          270
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Gln Pro Arg Val Val Pro Gln Thr Gln Glu Ser Gln Pro Asp Ser Asn
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<210> 263
 <211> 2554
 <212> DNA
 <213> Homo sapiens

<400> 263

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<210> 264

<211> 599

<212> PRT

<213> Homo sapiens

<400> 264

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Phe Gly Leu Asp Arg Tyr Gln Cys Asp Cys Thr Arg Thr Gly Tyr Ser
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277

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Leu	Arg	Glu	His	Asn	Arg	Val	Cys	Asp	Leu	Leu	Lys	Ala	Glu	His	Pro	305	310	315	320
Thr	Trp	Gly	Asp	Glu	Gln	Leu	Phe	Gln	Thr	Thr	Arg	Leu	Ile	Leu	Ile	325	330	335	
Gly	Glu	Thr	Ile	Lys	Ile	Val	Ile	Glu	Glu	Tyr	Val	Gln	Gln	Leu	Ser	340	345	350	
Gly	Tyr	Phe	Leu	Gln	Leu	Lys	Phe	Asp	Pro	Glu	Leu	Leu	Phe	Gly	Val	355	360	365	
Gln	Phe	Gln	Tyr	Arg	Asn	Arg	Ile	Ala	Met	Glu	Phe	Asn	His	Leu	Tyr	370	375	380	
His	Trp	His	Pro	Leu	Met	Pro	Asp	Ser	Phe	Lys	Val	Gly	Ser	Gln	Glu	385	390	395	400
Tyr	Ser	Tyr	Glu	Gln	Phe	Leu	Phe	Asn	Thr	Ser	Met	Leu	Val	Asp	Tyr	405	410	415	
Gly	Val	Glu	Ala	Leu	Val	Asp	Ala	Phe	Ser	Arg	Gln	Ile	Ala	Gly	Arg	420	425	430	
Ile	Gly	Gly	Gly	Arg	Asn	Met	Asp	His	His	Ile	Leu	His	Val	Ala	Val	435	440	445	
Asp	Val	Ile	Arg	Glu	Ser	Arg	Glu	Met	Arg	Leu	Gln	Pro	Phe	Asn	Glu	450	455	460	
Tyr	Arg	Lys	Arg	Phe	Gly	Met	Lys	Pro	Tyr	Thr	Ser	Phe	Gln	Glu	Leu	465	470	475	480
Val	Gly	Glu	Lys	Glu	Met	Ala	Ala	Glu	Leu	Glu	Glu	Leu	Tyr	Gly	Asp	485	490	495	
Ile	Asp	Ala	Leu	Glu	Phe	Tyr	Pro	Gly	Leu	Leu	Leu	Glu	Lys	Cys	His	500	505	510	
Pro	Asn	Ser	Ile	Phe	Gly	Glu	Ser	Met	Ile	Glu	Ile	Gly	Ala	Pro	Phe	515	520	525	

Ser Leu Lys Gly Leu Leu Gly Asn Pro Ile Cys Ser Pro Glu Tyr Trp
 530 535 540
 Lys Pro Ser Thr Phe Gly Gly Glu Val Gly Phe Asn Ile Val Lys Thr
 545 550 555 560
 Ala Thr Leu Lys Lys Leu Val Cys Leu Asn Thr Lys Thr Cys Pro Tyr
 565 570 575
 Val Ser Phe Arg Val Pro Asp Ala Ser Gln Asp Asp Gly Pro Ala Val
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 Glu Arg Pro Ser Thr Glu Leu
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<210> 265
 <211> 3000
 <212> DNA
 <213> Homo sapiens

<400> 265
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 agaaatggaa agtacagact tctgaaaata tctattgaaa atgagcaact tgtgattgga 180
 tcatatagtc agccttcaga ttccctgggat aaggattatg attcctttgt tttacccttg 240
 ttggaggaca aacaaccatg ctatatatta ttccaggtag attctcagaa tgcccaggga 300
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 tatgcagcaa caagagcaac tctgaagaag gaatttggag gtggccacat taaagatgaa 420
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279

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tcacgtttta cagtatgttt tagttggcag tatcatacct agatggtgaa taacatattc 2880
ccagtaaatt tatatagcag tgaagaatta catgccttct ggtggacatt ttataagtgc 2940
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<210> 266

<211> 350

<212> PRT

<213> Homo sapiens

<400> 266

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Phe Ala Arg Ala Arg Asn Gly Lys Tyr Arg Leu Leu Lys Ile Ser Ile
 20          25          30
Glu Asn Glu Gln Leu Val Ile Gly Ser Tyr Ser Gln Pro Ser Asp Ser
 35          40          45
Trp Asp Lys Asp Tyr Asp Ser Phe Val Leu Pro Leu Leu Glu Asp Lys
 50          55          60
Gln Pro Cys Tyr Ile Leu Phe Arg Leu Asp Ser Gln Asn Ala Gln Gly
 65          70          75          80
Tyr Glu Trp Ile Phe Ile Ala Trp Ser Pro Asp His Ser His Val Arg
 85          90          95
Gln Lys Met Leu Tyr Ala Ala Thr Arg Ala Thr Leu Lys Lys Glu Phe
100          105          110
Gly Gly Gly His Ile Lys Asp Glu Val Phe Gly Thr Val Lys Glu Asp
115          120          125
Val Ser Leu His Gly Tyr Lys Lys Tyr Leu Leu Ser Gln Ser Ser Pro
130          135          140
Ala Pro Leu Thr Ala Ala Glu Glu Glu Leu Arg Gln Ile Lys Ile Asn
145          150          155          160
Glu Val Gln Thr Asp Val Gly Val Asp Thr Lys His Gln Thr Leu Gln
165          170          175
Gly Val Ala Phe Pro Ile Ser Arg Glu Ala Phe Gln Ala Leu Glu Lys
180          185          190
Leu Asn Asn Arg Gln Leu Asn Tyr Val Gln Leu Glu Ile Asp Ile Lys
195          200          205
Asn Glu Ile Ile Ile Leu Ala Asn Thr Thr Asn Thr Glu Leu Lys Asp
210          215          220
Leu Pro Lys Arg Ile Pro Lys Asp Ser Ala Arg Tyr His Phe Phe Leu
225          230          235          240
Tyr Lys His Ser His Glu Gly Asp Tyr Leu Glu Ser Ile Val Phe Ile
245          250          255
Tyr Ser Met Pro Gly Tyr Thr Cys Ser Ile Arg Glu Arg Met Leu Tyr
260          265          270
Ser Ser Cys Lys Ser Arg Leu Leu Glu Ile Val Glu Arg Gln Leu Gln
275          280          285
Met Asp Val Ile Arg Lys Ile Glu Ile Asp Asn Gly Asp Glu Leu Thr
290          295          300
Ala Asp Phe Leu Tyr Glu Glu Val His Pro Lys Gln His Ala His Lys
305          310          315          320

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281

<210> 270
 <211> 94
 <212> PRT
 <213> Homo sapiens

<400> 270
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 20 25 30
 Glu Leu Lys Glu Leu Leu Gln Thr Glu Leu Ser Gly Phe Leu Asp Ala
 35 40 45
 Gln Lys Asp Val Asp Ala Val Asp Lys Val Met Lys Glu Leu Asp Glu
 50 55 60
 Asn Gly Asp Gly Glu Val Asp Phe Gln Glu Tyr Val Val Leu Val Ala
 65 70 75 80
 Ala Leu Thr Val Ala Cys Asn Asn Phe Phe Trp Glu Asn Ser
 85 90

<210> 271
 <211> 595
 <212> DNA
 <213> Homo sapiens

<400> 271
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 tcccagaagc ggacctgagg accccttggc cctggccttc aaaccaccc cctttccttc 480
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<210> 272
 <211> 105
 <212> PRT
 <213> Homo sapiens

<400> 272
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 20 25 30
 Thr Leu Ser Lys Thr Glu Phe Leu Ser Phe Met Asn Thr Glu Leu Ala
 35 40 45
 Ala Phe Thr Lys Asn Gln Lys Asp Pro Gly Val Leu Asp Arg Met Met
 50 55 60
 Lys Lys Leu Asp Thr Asn Ser Asp Gly Gln Leu Asp Phe Ser Glu Phe
 65 70 75 80
 Leu Asn Leu Ile Gly Gly Leu Ala Met Ala Cys His Asp Ser Phe Leu
 85 90 95
 Lys Ala Val Pro Ser Gln Lys Arg Thr
 100 105

282

<210> 273
 <211> 428
 <212> DNA
 <213> Homo sapiens

<400> 273
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 tgacttcttc cagggctgcc cagaccgacc ctgaagcaga actcttgact tcctgccatg 360
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<210> 274
 <211> 97
 <212> PRT
 <213> Homo sapiens

<400> 274
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 20 25 30
 Glu Met Lys Glu Leu Leu His Lys Glu Leu Pro Ser Phe Val Gly Glu
 35 40 45
 Lys Val Asp Glu Glu Gly Leu Lys Lys Leu Met Gly Ser Leu Asp Glu
 50 55 60
 Asn Ser Asp Gln Gln Val Asp Phe Gln Glu Tyr Ala Val Phe Leu Ala
 65 70 75 80
 Leu Ile Thr Val Met Cys Asn Asp Phe Phe Gln Gly Cys Pro Asp Arg
 85 90 95
 Pro

<210> 275
 <211> 470
 <212> DNA
 <213> Homo sapiens

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 caggccattg gcctcctcgt ggccatcttc cacaagtact ccggcaggga gggtgacaag 180
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 gccctcaagg gctgaaaata aatagggaag atggagacac ctctgggggt cctctctgag 420
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<210> 276
 <211> 90
 <212> PRT
 <213> Homo sapiens

<400> 276

Met	Ala	Cys	Pro	Leu	Asp	Gln	Ala	Ile	Gly	Leu	Leu	Val	Ala	Ile	Phe
1				5					10					15	
His	Lys	Tyr	Ser	Gly	Arg	Glu	Gly	Asp	Lys	His	Thr	Leu	Ser	Lys	Lys
			20					25					30		
Glu	Leu	Lys	Glu	Leu	Ile	Gln	Lys	Glu	Leu	Thr	Ile	Gly	Ser	Lys	Leu
		35					40					45			
Gln	Asp	Ala	Glu	Ile	Ala	Arg	Leu	Met	Glu	Asp	Leu	Asp	Arg	Asn	Lys
	50					55					60				
Asp	Gln	Glu	Val	Asn	Phe	Gln	Glu	Tyr	Val	Thr	Phe	Leu	Gly	Ala	Leu
65					70					75					80
Ala	Leu	Ile	Tyr	Asn	Glu	Ala	Leu	Lys	Gly						
				85					90						

<210> 277

<211> 3151

<212> DNA

<213> Homo sapiens

<400> 277

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<210> 278

<211> 669

<212> PRT

<213> Homo sapiens

<400> 278

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20      25      30
Pro Glu Pro Ala Ala Pro Gln Gln Pro Thr Ala Glu Glu Glu Ala Leu
35      40      45
Ile Glu Phe His Arg Ser Tyr Arg Glu Leu Phe Glu Phe Phe Cys Asn
50      55      60
Asn Thr Thr Ile His Gly Ala Ile Arg Leu Val Cys Ser Gln His Asn
65      70      75      80
Arg Met Lys Thr Ala Phe Trp Ala Val Leu Trp Leu Cys Thr Phe Gly
85      90      95
Met Met Tyr Trp Gln Phe Gly Leu Leu Phe Gly Glu Tyr Phe Ser Tyr
100     105     110
Pro Val Ser Leu Asn Ile Asn Leu Asn Ser Asp Lys Leu Val Phe Pro
115     120     125
Ala Val Thr Ile Cys Thr Leu Asn Pro Tyr Arg Tyr Pro Glu Ile Lys
130     135     140
Glu Glu Leu Glu Glu Leu Asp Arg Ile Thr Glu Gln Thr Leu Phe Asp
145     150     155     160
Leu Tyr Lys Tyr Ser Ser Phe Thr Thr Leu Val Ala Gly Ser Arg Ser
165     170     175
Arg Arg Asp Leu Arg Gly Thr Leu Pro His Pro Leu Gln Arg Leu Arg
180     185     190
Val Pro Pro Pro Pro His Gly Ala Arg Arg Ala Arg Ser Val Ala Ser
195     200     205
Ser Leu Arg Asp Asn Asn Pro Gln Val Asp Trp Lys Asp Trp Lys Ile
210     215     220
Gly Phe Gln Leu Cys Asn Gln Asn Lys Ser Asp Cys Phe Tyr Gln Thr
225     230     235     240
Tyr Ser Ser Gly Val Asp Ala Val Arg Glu Trp Tyr Arg Phe His Tyr
245     250     255
Ile Asn Ile Leu Ser Arg Leu Pro Glu Thr Leu Pro Ser Leu Glu Glu
260     265     270

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285

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Cys	Asn	Gln	Ala	Asn	Tyr	Ser	His	Phe	His	His	Pro	Met	Tyr	Gly	Asn
		290				295					300				
Cys	Tyr	Thr	Phe	Asn	Asp	Lys	Asn	Asn	Ser	Asn	Leu	Trp	Met	Ser	Ser
305				310						315					320
Met	Pro	Gly	Ile	Asn	Asn	Gly	Leu	Ser	Leu	Met	Leu	Arg	Ala	Glu	Gln
				325					330					335	
Asn	Asp	Phe	Ile	Pro	Leu	Leu	Ser	Thr	Val	Thr	Gly	Ala	Arg	Val	Met
			340					345					350		
Val	His	Gly	Gln	Asp	Glu	Pro	Ala	Phe	Met	Asp	Asp	Gly	Gly	Phe	Asn
		355					360					365			
Leu	Arg	Pro	Gly	Val	Glu	Thr	Ser	Ile	Ser	Met	Arg	Lys	Glu	Thr	Leu
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Asp	Arg	Leu	Gly	Gly	Asp	Tyr	Gly	Asp	Cys	Thr	Lys	Asn	Gly	Ser	Asp
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<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(3174)

<223> n = A,T,C or G

<400> 279

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 <211> 669
 <212> PRT
 <213> Homo sapiens

<400> 280

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Asn	Asp	Phe	Ile	Pro	Leu	Leu	Ser	Thr	Val	Thr	Gly	Ala	Arg	Val	Met
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Asp	Arg	Leu	Gly	Gly	Asp	Tyr	Gly	Asp	Cys	Thr	Lys	Asn	Gly	Ser	Asp
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Val	Pro	Val	Glu	Asn	Leu	Tyr	Pro	Ser	Lys	Tyr	Thr	Gln	Gln	Val	Cys

288

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Lys	His	Ser	Ser	Trp	Gly	Tyr	Cys	Tyr	Tyr	Lys	Leu	Gln	Val	Asp	Phe
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Pro	Pro	Ala	Tyr	Ala	Thr	Leu	Gly	Pro	Arg	Pro	Ser	Pro	Gly	Gly	Ser
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<210> 281

<211> 2892

<212> DNA

<213> Homo sapiens

<400> 281

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<211> 176

<212> PRT

<213> Homo sapiens

<400> 282

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Gln Gly Trp Val Met Phe Val Ser Val Thr Ala Phe Phe Phe Ser Leu
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Gln Tyr Asn Ile Asn Val Ala Ala Ser Ile Phe Ala Phe Met Thr Thr

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<210>	284
<211>	771
<212>	PRT

<213> Homo sapiens

<400> 284

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Lys Leu Ser Tyr Lys Glu Met Leu Glu Ser Asn Asn Val Ile Thr Phe
          35           40           45
Asn Gly Leu Ala Asn Ser Ser Ser Tyr His Thr Phe Leu Leu Asp Glu
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Glu Arg Ser Arg Leu Tyr Val Gly Ala Lys Asp His Ile Phe Ser Phe
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Asp Leu Val Asn Ile Lys Asp Phe Gln Lys Ile Val Trp Pro Val Ser
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Tyr Thr Arg Arg Asp Glu Cys Lys Trp Ala Gly Lys Asp Ile Leu Lys
          100          105          110
Glu Cys Ala Asn Phe Ile Lys Val Leu Lys Ala Tyr Asn Gln Thr His
          115          120          125
Leu Tyr Ala Cys Gly Thr Gly Ala Phe His Pro Ile Cys Thr Tyr Ile
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Glu Ile Gly His His Pro Glu Asp Asn Ile Phe Lys Leu Glu Asn Ser
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His Phe Glu Asn Gly Arg Gly Lys Ser Pro Tyr Asp Pro Lys Leu Leu
          165          170          175
Thr Ala Ser Leu Leu Ile Asp Gly Glu Leu Tyr Ser Gly Thr Ala Ala
          180          185          190
Asp Phe Met Gly Arg Asp Phe Ala Ile Phe Arg Thr Leu Gly His His
          195          200          205
His Pro Ile Arg Thr Glu Gln His Asp Ser Arg Trp Leu Asn Asp Pro
          210          215          220
Lys Phe Ile Ser Ala His Leu Ile Ser Glu Ser Asp Asn Pro Glu Asp
          225          230          235          240
Asp Lys Val Tyr Phe Phe Phe Arg Glu Asn Ala Ile Asp Gly Glu His
          245          250          255
Ser Gly Lys Ala Thr His Ala Arg Ile Gly Gln Ile Cys Lys Asn Asp
          260          265          270
Phe Gly Gly His Arg Ser Leu Val Asn Lys Trp Thr Thr Phe Leu Lys
          275          280          285
Ala Arg Leu Ile Cys Ser Val Pro Gly Pro Asn Gly Ile Asp Thr His
          290          295          300
Phe Asp Glu Leu Gln Asp Val Phe Leu Met Asn Phe Lys Asp Pro Lys
          305          310          315          320
Asn Pro Val Val Tyr Gly Val Phe Thr Thr Ser Ser Asn Ile Phe Lys
          325          330          335
Gly Ser Ala Val Cys Met Tyr Ser Met Ser Asp Val Arg Arg Val Phe
          340          345          350
Leu Gly Pro Tyr Ala His Arg Asp Gly Pro Asn Tyr Gln Trp Val Pro
          355          360          365
Tyr Gln Gly Arg Val Pro Tyr Pro Arg Pro Gly Thr Cys Pro Ser Lys
          370          375          380
Thr Phe Gly Gly Phe Asp Ser Thr Lys Asp Leu Pro Asp Asp Val Ile
          385          390          395          400
Thr Phe Ala Arg Ser His Pro Ala Met Tyr Asn Pro Val Phe Pro Met
          405          410          415
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<210> 285
<211> 3041
<212> DNA
<213> Homo sapiens
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<400> 285						
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<210> 286

<211> 418

<212> PRT

<213> Homo sapiens

<400> 286

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Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
          35          40          45
Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln

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294

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			85						90					95	
His	Asp	Glu	Ile	Leu	Glu	Gly	Leu	Asn	Phe	Asn	Leu	Thr	Glu	Ile	Pro
			100					105					110		
Glu	Ala	Gln	Ile	His	Glu	Gly	Phe	Gln	Glu	Leu	Leu	Arg	Thr	Leu	Asn
		115					120					125			
Gln	Pro	Asp	Ser	Gln	Leu	Gln	Leu	Thr	Thr	Gly	Asn	Gly	Leu	Phe	Leu
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Ser	Glu	Gly	Leu	Lys	Leu	Val	Asp	Lys	Phe	Leu	Glu	Asp	Val	Lys	Lys
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Leu	Tyr	His	Ser	Glu	Ala	Phe	Thr	Val	Asn	Phe	Gly	Asp	Thr	Glu	Glu
			165						170					175	
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Lys	Asp	Thr	Glu	Glu	Glu	Asp	Phe	His	Val	Asp	Gln	Val	Thr	Thr	Val
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Lys	Val	Pro	Met	Met	Lys	Arg	Leu	Gly	Met	Phe	Asn	Ile	Gln	His	Cys
			245						250					255	
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		260						265					270		
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	275						280					285			
Asn	Glu	Leu	Thr	His	Asp	Ile	Ile	Thr	Lys	Phe	Leu	Glu	Asn	Glu	Asp
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Arg	Arg	Ser	Ala	Ser	Leu	His	Leu	Pro	Lys	Leu	Ser	Ile	Thr	Gly	Thr
305					310					315					320
Tyr	Asp	Leu	Lys	Ser	Val	Leu	Gly	Gln	Leu	Gly	Ile	Thr	Lys	Val	Phe
			325						330					335	
Ser	Asn	Gly	Ala	Asp	Leu	Ser	Gly	Val	Thr	Glu	Glu	Ala	Pro	Leu	Lys
		340						345					350		
Leu	Ser	Lys	Ala	Val	His	Lys	Ala	Val	Leu	Thr	Ile	Asp	Glu	Lys	Gly
	355						360					365			
Thr	Glu	Ala	Ala	Gly	Ala	Met	Phe	Leu	Glu	Ala	Ile	Pro	Met	Ser	Ile
	370					375					380				
Pro	Pro	Glu	Val	Lys	Phe	Asn	Lys	Pro	Phe	Val	Phe	Leu	Met	Ile	Glu
385					390					395					400
Gln	Asn	Thr	Lys	Ser	Pro	Leu	Phe	Met	Gly	Lys	Val	Val	Asn	Pro	Thr
			405						410					415	

Gln Lys

<210> 287
 <211> 3928
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (1)...(3928)
 <223> n = A,T,C or G

<400> 287

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296

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<210> 288
 <211> 293
 <212> PRT
 <213> Homo sapiens

<400> 288

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			20					25					30		
Trp	Asn	Trp	Ile	Trp	Arg	Arg	Cys	Cys	Arg	Ala	Ala	Ser	Ala	Ala	Val
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Ser	Phe	Ser	Asp	Ile	Ala	Ser	Leu	Val	Val	Trp	Cys	Met	Ala	Val	Gly
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Pro	Glu	Asp	Gly	Lys	Ala	Asp	Ile	Val	Arg	Ala	Ala	Gln	Asp	Phe	Cys
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Gln	Leu	Val	Ala	Gln	Lys	Gln	Lys	Arg	Pro	Thr	Asp	Leu	Asp	Val	Asp
	210					215					220				
Thr	Leu	Ala	Ser	Leu	Leu	Ser	Ser	Asn	Gly	Cys	Pro	Asp	Pro	Asp	Leu
225					230					235					240
Val	Leu	Lys	Phe	Gly	Pro	Val	Asp	Ser	Thr	Leu	Gly	Phe	Leu	Pro	Trp
			245						250					255	
His	Ile	Arg	Leu	Thr	Glu	Ile	Val	Ser	Leu	Pro	Ser	His	Leu	Asn	Ile
			260					265					270		
Ser	Tyr	Glu	Asp	Phe	Phe	Ser	Ala	Leu	Arg	Gln	Tyr	Ala	Ala	Cys	Glu
	275						280					285			
Gln	Arg	Leu	Gly	Lys											
	290														

<210> 289

<211> 936
 <212> DNA
 <213> Homo sapiens

<400> 289
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 ctggggtatga cctgtcagcc tctacattct ctcctgacgg aagagttttt caagttgaat 120
 atgctatgaa ggctgtggaa aatagtagta cagctattgg aatcagatgc aaagatgggtg 180
 ttgtcttttg ggtagaaaaa ttagtccttt ctaaacttta tgaagaaggt tccaacaaaa 240
 gacttttttaa tgttgatcgg catgttgaa tggcagtagc aggtttgttg gcagatgctc 300
 gttcttttagc agacatagca agagaagaag cttccaactt cagatctaac tttggctaca 360
 acattccact aaaacatctt gcagacagag tggccatgta tgtgcatgca tatacactct 420
 acagtgtctgt tagacctttt ggctgcagtg tgaatgacgg tgcgcaactc tacatgattg 480
 acccatcagg tgtttcatcac gggtattggg gctgtgccat cggcaaagcc aggcaagctg 540
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 aagttgcaaa aataattttac atagtacatg acgaagttaa ggataaagct tttgaactag 660
 aactcagctg ggttggtgaa ttaactaatg gaagacatga aattgttcca aaagatataa 720
 gagaagaagc agagaaatat gctaaggaat ctctgaagga agaagatgaa tcagatgatg 780
 ataatatgta acattttactc cagcatctat tgtattttta atttctactc cagtccaatg 840
 taactattta gccctggatt atacatactg tccaattttc attaaatttt tgtcttataa 900
 ctattaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa 936

<210> 290
 <211> 248
 <212> PRT
 <213> Homo sapiens

<400> 290
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 20 25 30
 Asn Ser Ser Thr Ala Ile Gly Ile Arg Cys Lys Asp Gly Val Val Phe
 35 40 45
 Gly Val Glu Lys Leu Val Leu Ser Lys Leu Tyr Glu Glu Gly Ser Asn
 50 55 60
 Lys Arg Leu Phe Asn Val Asp Arg His Val Gly Met Ala Val Ala Gly
 65 70 75 80
 Leu Leu Ala Asp Ala Arg Ser Leu Ala Asp Ile Ala Arg Glu Glu Ala
 85 90 95
 Ser Asn Phe Arg Ser Asn Phe Gly Tyr Asn Ile Pro Leu Lys His Leu
 100 105 110
 Ala Asp Arg Val Ala Met Tyr Val His Ala Tyr Thr Leu Tyr Ser Ala
 115 120 125
 Val Arg Pro Phe Gly Cys Ser Val Asn Asp Gly Ala Gln Leu Tyr Met
 130 135 140
 Ile Asp Pro Ser Gly Val Ser Tyr Gly Tyr Trp Gly Cys Ala Ile Gly
 145 150 155 160
 Lys Ala Arg Gln Ala Ala Lys Thr Glu Ile Glu Lys Leu Gln Met Lys
 165 170 175
 Glu Met Thr Cys Arg Asp Ile Val Lys Glu Val Ala Lys Ile Ile Tyr
 180 185 190
 Ile Val His Asp Glu Val Lys Asp Lys Ala Phe Glu Leu Glu Leu Ser
 195 200 205
 Trp Val Gly Glu Leu Thr Asn Gly Arg His Glu Ile Val Pro Lys Asp
 210 215 220
 Ile Arg Glu Glu Ala Glu Lys Tyr Ala Lys Glu Ser Leu Lys Glu Glu
 225 230 235 240

Asp Glu Ser Asp Asp Asn Met
245

<210> 291
<211> 2782
<212> DNA
<213> Homo sapiens

<400> 291
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gaaaccttca ggaacctggc ttctgttaga aaacaatggg aagaccagaa cattgaagac 300
ccattcaaaa ttcccaggag aaatataagt catattccag agagactctg tgaaagtaaa 360
gaaggtgggtc aaggtgaaga aaccttcagc cagattccag atggtattct gaacaagaaa 420
actcctggag taaaaccgtg tgaaagcagt gtgtgtggag aagttggcat gggctccttca 480
tcacttaata ggcacatcag agatcacact ggacgtgaac caaatgaata tcaggaatat 540
tgaaagaagt catatacacg taaccagtg ggacgagcct tgagttatca tcgctctttt 600
ccagtacgtg aaaggactca tcctggagga aagccctatg attgtaagga atgtggagaa 660
acctttattt ctcttgaag cattcgaaga cacatgttaa cgcatagggg aggtgtacct 720
tacaaatgta aggtgtgtgg gaaagccttt gattatccca gtttatttcg tatacatgaa 780
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<210> 292
 <211> 461
 <212> PRT
 <213> Homo sapiens

<400> 292

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Glu	Trp	Ala	Leu	Leu	Asp	Pro	Ser	Gln	Lys	Asn	Leu	Tyr	Arg	Asp	Val
		20						25					30		
Met	Arg	Glu	Thr	Phe	Arg	Asn	Leu	Ala	Ser	Val	Gly	Lys	Gln	Trp	Glu
		35					40					45			
Asp	Gln	Asn	Ile	Glu	Asp	Pro	Phe	Lys	Ile	Pro	Arg	Arg	Asn	Ile	Ser
	50					55					60				
His	Ile	Pro	Glu	Arg	Leu	Cys	Glu	Ser	Lys	Glu	Gly	Gly	Gln	Gly	Glu
65					70					75					80
Glu	Thr	Phe	Ser	Gln	Ile	Pro	Asp	Gly	Ile	Leu	Asn	Lys	Lys	Thr	Pro
			85					90						95	
Gly	Val	Lys	Pro	Cys	Glu	Ser	Ser	Val	Cys	Gly	Glu	Val	Gly	Met	Gly
			100					105					110		
Pro	Ser	Ser	Leu	Asn	Arg	His	Ile	Arg	Asp	His	Thr	Gly	Arg	Glu	Pro
		115					120					125			
Asn	Glu	Tyr	Gln	Glu	Tyr	Gly	Lys	Lys	Ser	Tyr	Thr	Arg	Asn	Gln	Cys
	130					135					140				
Gly	Arg	Ala	Leu	Ser	Tyr	His	Arg	Ser	Phe	Pro	Val	Arg	Glu	Arg	Thr
145					150					155					160
His	Pro	Gly	Gly	Lys	Pro	Tyr	Asp	Cys	Lys	Glu	Cys	Gly	Glu	Thr	Phe
			165						170					175	
Ile	Ser	Leu	Val	Ser	Ile	Arg	Arg	His	Met	Leu	Thr	His	Arg	Gly	Gly
		180						185					190		
Val	Pro	Tyr	Lys	Cys	Lys	Val	Cys	Gly	Lys	Ala	Phe	Asp	Tyr	Pro	Ser
		195					200					205			
Ileu	Phe	Arg	Ile	His	Glu	Arg	Ser	His	Thr	Gly	Glu	Lys	Pro	Tyr	Glu
	210					215					220				
Cys	Lys	Gln	Cys	Gly	Lys	Ala	Phe	Ser	Cys	Ser	Ser	Tyr	Ile	Arg	Ile
225					230					235					240
His	Glu	Arg	Thr	His	Thr	Gly	Asp	Lys	Pro	Tyr	Glu	Cys	Lys	Gln	Cys
			245						250					255	
Gly	Lys	Ala	Phe	Ser	Cys	Ser	Lys	Tyr	Ile	Arg	Ile	His	Glu	Arg	Thr
		260					265						270		
His	Thr	Gly	Glu	Lys	Pro	Tyr	Glu	Cys	Lys	Gln	Cys	Gly	Lys	Ala	Phe
		275					280					285			
Arg	Cys	Ala	Ser	Ser	Val	Arg	Ser	His	Glu	Arg	Thr	His	Thr	Gly	Glu
	290					295					300				
Lys	Leu	Phe	Glu	Cys	Lys	Glu	Cys	Gly	Lys	Ala	Leu	Thr	Cys	Leu	Ala
305					310					315					320
Ser	Val	Arg	Arg	His	Met	Ile	Lys	His	Thr	Gly	Asn	Gly	Pro	Tyr	Lys
			325						330					335	
Cys	Lys	Val	Cys	Gly	Lys	Ala	Phe	Asp	Phe	Pro	Ser	Ser	Phe	Arg	Ile
		340					345						350		
His	Glu	Arg	Thr	His	Thr	Gly	Glu	Lys	Pro	Tyr	Asp	Cys	Lys	Gln	Cys
		355				360						365			
Gly	Lys	Ala	Phe	Ser	Cys	Ser	Ser	Ser	Phe	Arg	Lys	His	Glu	Arg	Ile
	370					375					380				
His	Thr	Gly	Glu	Lys	Pro	Tyr	Lys	Cys	Thr	Lys	Cys	Gly	Lys	Ala	Phe
385					390					395					400
Ser	Arg	Ser	Ser	Tyr	Phe	Arg	Ile	His	Glu	Arg	Thr	His	Thr	Gly	Glu
				405					410					415	

300

Lys Pro Tyr Glu Cys Lys Gln Cys Gly Lys Ala Phe Ser Arg Ser Thr
 420 425 430
 Tyr Phe Arg Val His Glu Lys Ile His Thr Gly Glu Lys Pro Tyr Glu
 435 440 445
 Asn Pro Asn Pro Asn Ala Ser Val Val Pro Val Leu Ser
 450 455 460

<210> 293
 <211> 666
 <212> DNA
 <213> Homo sapiens

<400> 293
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 atagttgctg tggtggcctc atagccttac ctggcatagg aaagataaac aatctccttg 120
 gtgtcaggat ttctgggtctc tggctagggtt tcctgcttat gcaatagtag ctgggagagg 180
 ccgaaagaat tctggtgggg ccacacccac tggtgaaaga ataaatagtg aggtttggca 240
 ttggccatca gagtcactcc tgccttcacc atgaagtcca gcggcctctt ccccttcctg 300
 gtgctgcttg ccctgggaac tctggcacct tgggctgtgg aaggctctgg aaagtgttaag 360
 ttggagtcac tctggtctaa tctgggctgc agggctcagag gtgggggtctc cttgtggtgt 420
 ggggtgtgtcc ccttctgtag gctctgatcc ctcagcttag tttcgggaga cctccctgag 480
 ggtggaatac atgtctggct gagctccaag gtttgtgtga cagtttgagc ttctggaaat 540
 gcttcctcta tgcagccatg ctgtcagccc aggtccact ctctctctct ctctctctct 600
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 aaaaaa 666

<210> 294
 <211> 58
 <212> PRT
 <213> Homo sapiens

<400> 294
 Met Lys Ser Ser Gly Leu Phe Pro Phe Leu Val Leu Leu Ala Leu Gly
 1 5 10 15
 Thr Leu Ala Pro Trp Ala Val Glu Gly Ser Gly Lys Cys Lys Leu Glu
 20 25 30
 Ser Leu Trp Ser Asn Leu Gly Cys Arg Val Arg Gly Gly Val Ser Leu
 35 40 45
 Trp Cys Gly Cys Val Pro Phe Cys Arg Leu
 50 55

<210> 295
 <211> 594
 <212> DNA
 <213> Homo sapiens

<400> 295
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 tgtcctccta agaaatctgc ccagtgcctt agatacaaga aacctgagtg ccagagtgac 180
 tggcagtgctc cagggaagaa gagatgttgt cctgacactt gtggcatcaa atgcctggat 240
 cctgttgaca ccccaaacc aacaaggagg aagcctggga agtgcccagt gacttatggc 300
 caatgtttga tgcttaacc cccaatttc tgtgagatgg atggccagt caagcgtgac 360
 ttgaagtgtt gcatgggcat gtgtgggaaa tcctgcgttt cccctgtgaa agcttgattc 420
 ctgccatatg gaggaggctc tggagtctgt ctctgtgtgg tccaggtoct ttccaccctg 480
 agacttggct ccaccactga tctcctcctt tggggaaagg cttggcacac agcaggcttt 540

301

caagaagtgc cagttgatca atgaataaat aaacgagcct atttctcttt gcac 594

<210> 296

<211> 132

<212> PRT

<213> Homo sapiens

<400> 296

Met	Lys	Ser	Ser	Gly	Leu	Phe	Pro	Phe	Leu	Val	Leu	Leu	Ala	Leu	Gly
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Thr	Leu	Ala	Pro	Trp	Ala	Val	Glu	Gly	Ser	Gly	Lys	Ser	Phe	Lys	Ala
			20					25					30		
Gly	Val	Cys	Pro	Pro	Lys	Lys	Ser	Ala	Gln	Cys	Leu	Arg	Tyr	Lys	Lys
		35					40					45			
Pro	Glu	Cys	Gln	Ser	Asp	Trp	Gln	Cys	Pro	Gly	Lys	Lys	Arg	Cys	Cys
	50				55						60				
Pro	Asp	Thr	Cys	Gly	Ile	Lys	Cys	Leu	Asp	Pro	Val	Asp	Thr	Pro	Asn
65				70					75					80	
Pro	Thr	Arg	Arg	Lys	Pro	Gly	Lys	Cys	Pro	Val	Thr	Tyr	Gly	Gln	Cys
			85						90					95	
Leu	Met	Leu	Asn	Pro	Pro	Asn	Phe	Cys	Glu	Met	Asp	Gly	Gln	Cys	Lys
			100					105					110		
Arg	Asp	Leu	Lys	Cys	Cys	Met	Gly	Met	Cys	Gly	Lys	Ser	Cys	Val	Ser
		115					120					125			
Pro	Val	Lys	Ala												
			130												

<210> 297

<211> 720

<212> DNA

<213> Homo sapiens

<400> 297

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ggggtgacgg	aagcagctga	gaagaccaag	gaggggggtca	tgtatgtggg	agccaagacc	180
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gcggtgagcg	aggctgtggt	gagcagcgtc	aacactgtgg	ccaccaagac	cgtggaggag	300
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actgccctcc	ctcggcccca	cccacctctc	ggtccttctg	accccaactta	tgctgctgtg	660
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<210> 298

<211> 127

<212> PRT

<213> Homo sapiens

<400> 298

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Gly	Ala	Val	Glu	Lys	Thr	Lys	Gln	Gly	Val	Thr	Glu	Ala	Ala	Glu	Lys
			20					25					30		

302

Thr	Lys	Glu	Gly	Val	Met	Tyr	Val	Gly	Ala	Lys	Thr	Lys	Glu	Asn	Val
	35						40					45			
Val	Gln	Ser	Val	Thr	Ser	Val	Ala	Glu	Lys	Thr	Lys	Glu	Gln	Ala	Asn
	50					55					60				
Ala	Val	Ser	Glu	Ala	Val	Val	Ser	Ser	Val	Asn	Thr	Val	Ala	Thr	Lys
65					70					75					80
Thr	Val	Glu	Glu	Ala	Glu	Asn	Ile	Ala	Val	Thr	Ser	Gly	Val	Val	Arg
				85					90					95	
Lys	Glu	Asp	Leu	Arg	Pro	Ser	Ala	Pro	Gln	Gln	Glu	Gly	Val	Ala	Ser
			100					105					110		
Lys	Glu	Lys	Glu	Glu	Val	Ala	Glu	Glu	Ala	Gln	Ser	Gly	Gly	Asp	
		115					120					125			

<210> 299
 <211> 6981
 <212> DNA
 <213> Homo sapiens

<400> 299
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 ctgagccggc tctcctggcc tcgcgctgca cattctctcc tggcggcggc gccacctgca 180
 gtagcggttcg cccgaacatg gcgacacgga gcagcaggag ggagtcgcga ctcccgttcc 240
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 agccgctccg gaggaacgg agcgcctgcc tgcagcccga gcccatcaag gtgtacggac 480
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 agcggtagat ctttgcagac gcttatgcc agtacctctg gatcacgttt gacttctgca 780
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 ccactgtctt ccgaagtaca gatttcttcc agtcccggga aaaccaggaa gtgatccttg 1080
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 tgagagcagc ccagtttgtc acaagacatc ctattaatga atattacatc gcagatgcct 1260
 ccgaggacca ggtgtttgtg tgtgtcagcc acagtaacaa ccgcaccaat ttatacatct 1320
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 accgagtggg aggattgcaa ggagtctaca ttgctactct gattaatggt tctatgaatg 1500
 aggagaacat gagatcgggt atcacctttg acaaagggg aacctgggag tttcttcagg 1560
 ctccagcctt cacgggatat ggagagaaaa tcaattgtga gctttcccag ggctgttccc 1620
 ttcatctggc tcagcgctc agtcagctcc tcaacctcca gctccggaga atgcccattc 1680
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 ctgtcttcac catctttggc tcgaacaaag agaattgcca cagctggctg atcctccagg 2040
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304

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<211> 2214

<212> PRT

<213> Homo sapiens

<400> 300

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Gln Arg Leu His Gly Gly Ser Ala Pro Leu Pro Gln Asp Arg Gly Phe
          35          40          45
Leu Val Val Gln Gly Asp Pro Arg Glu Leu Arg Leu Trp Ala Arg Gly
          50          55          60
Asp Ala Arg Gly Ala Ser Arg Ala Asp Glu Lys Pro Leu Arg Arg Lys
65          70          75          80
Arg Ser Ala Ala Leu Gln Pro Glu Pro Ile Lys Val Tyr Gly Gln Val
          85          90          95
Ser Leu Asn Asp Ser His Asn Gln Met Val Val His Trp Ala Gly Glu
          100          105          110
Lys Ser Asn Val Ile Val Ala Leu Ala Arg Asp Ser Leu Ala Leu Ala
          115          120          125
Arg Pro Lys Ser Ser Asp Val Tyr Val Ser Tyr Asp Tyr Gly Lys Ser
          130          135          140
Phe Lys Lys Ile Ser Asp Lys Leu Asn Phe Gly Leu Gly Asn Arg Ser
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Glu Ala Val Ile Ala Gln Phe Tyr His Ser Pro Ala Asp Asn Lys Arg
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Tyr Ile Phe Ala Asp Ala Tyr Ala Gln Tyr Leu Trp Ile Thr Phe Asp
          180          185          190
Phe Cys Asn Thr Leu Gln Gly Phe Ser Ile Pro Phe Arg Ala Ala Asp
          195          200          205
Leu Leu Leu His Ser Lys Ala Ser Asn Leu Leu Leu Gly Phe Asp Arg
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Ser His Pro Asn Lys Gln Leu Trp Lys Ser Asp Asp Phe Gly Gln Thr
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305

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Lys	Glu	Ser	Ala	Pro	Gly	Leu	Ile	Ile	Ala	Thr	Gly	Ser	Val	Gly	Lys
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 His Leu His Val Val His Thr Gly Lys Thr Ser Val Val Ile Lys Trp
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 Glu Ser Pro Tyr Asp Ser Pro Asp Gln Asp Leu Leu Tyr Ala Ile Ala
 1955 1960 1965
 Val Lys Asp Leu Ile Arg Lys Thr Asp Arg Ser Tyr Lys Val Lys Ser
 1970 1975 1980
 Arg Asn Ser Thr Val Glu Tyr Thr Leu Asn Lys Leu Glu Pro Gly Gly
 1985 1990 1995 2000
 Lys Tyr His Ile Ile Val Gln Leu Gly Asn Met Ser Lys Asp Ser Ser
 2005 2010 2015
 Ile Lys Ile Thr Thr Val Ser Leu Ser Ala Pro Asp Ala Leu Lys Ile
 2020 2025 2030
 Ile Thr Glu Asn Asp His Val Leu Leu Phe Trp Lys Ser Leu Ala Leu
 2035 2040 2045
 Lys Glu Lys His Phe Asn Glu Ser Arg Gly Tyr Glu Ile His Met Phe
 2050 2055 2060
 Asp Ser Ala Met Asn Ile Thr Ala Tyr Leu Gly Asn Thr Thr Asp Asn
 2065 2070 2075 2080
 Phe Phe Lys Ile Ser Asn Leu Lys Met Gly His Asn Tyr Thr Phe Thr
 2085 2090 2095

309

Val Gln Ala Arg Cys Leu Phe Gly Asn Gln Ile Cys Gly Glu Pro Ala
 2100 2105 2110
 Ile Leu Leu Tyr Asp Glu Leu Gly Ser Gly Ala Asp Ala Ser Ala Thr
 2115 2120 2125
 Gln Ala Ala Arg Ser Thr Asp Val Ala Ala Val Val Val Pro Ile Leu
 2130 2135 2140
 Phe Leu Ile Leu Leu Ser Leu Gly Val Gly Phe Ala Ile Leu Tyr Thr
 2145 2150 2155 2160
 Lys His Arg Arg Leu Gln Ser Ser Phe Thr Ala Phe Ala Asn Ser His
 2165 2170 2175
 Tyr Ser Ser Arg Leu Gly Ser Ala Ile Phe Ser Ser Gly Asp Asp Leu
 2180 2185 2190
 Gly Glu Asp Asp Glu Asp Ala Pro Met Ile Thr Gly Phe Ser Asp Asp
 2195 2200 2205
 Val Pro Met Val Ile Ala
 2210

<210> 301
 <211> 1544
 <212> DNA
 <213> Homo sapiens

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 ccacactgaa ggtccggaag ggcgacttcc gggggctttg gcacctggcg gacctcccgc 180
 gagegtcggc acctgaacgc gaggcgctcc attgcgctg cgcgttgagg ggcttcccgc 240
 acctgatcgc gagaccccaa cggctggttg cgtgcctgc gcgtctcggc tgagctggcc 300
 atggcgcagc tgtgcgggct gaggcggagc cgggcgtttc tcgccctgct gggatcgctg 360
 ctctctctctg gggtcctggc ggccgaccga gaacgcagca tccacgactt ctgcctggtg 420
 tcgaaggttg tgggcagatg ccgggcctcc atgcctaggt ggtggtacaa tgtcactgac 480
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 ccttgccgtg catccttccc acgctgggtac tttgacgtgg agaggaactc ctgcaataac 780
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 tggcagggat gggtttgctt tggaatcct ctaggaggct cctcctcgca tggcctgcag 1260
 tctggcagca gccccgagtt gtttcctcgc tgatcgattt ctttcctcca ggtagagttt 1320
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 cgtttctttt gtttgtctga tttatggttt ttttaagtat aaacaaaagt tttttattag 1440
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 aataaatttc cagcatgttg ctttcaaaaa aaaaaaaaaa aaaa 1544

<210> 302
 <211> 252

310

<212> PRT

<213> Homo sapiens

<400> 302

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          20          25          30
Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg
          35          40          45
Ala Ser Met Pro Arg Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln
          50          55          60
Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr
65          70          75          80
Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr
          85          90          95
Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser
          100          105          110
Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn
          115          120          125
Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala
          130          135          140
Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn
145          150          155          160
Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Glu
          165          170          175
Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu
          180          185          190
Pro Leu Gly Ser Lys Val Val Val Leu Ala Gly Leu Phe Val Met Val
          195          200          205
Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr Leu Ile Arg Val Ala
          210          215          220
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Asp Lys Glu Gln Leu Val Lys Asn Thr Tyr Val Leu
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<210> 303

<211> 1558

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

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<223> n = A,T,C or G

<400> 303

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aggcatcgcg cgccgagaag gccggggcgtc cccacactga aggtccggaa aggcgacttc 180
cgggggcttt ggcaacctggc ggacctccc ggagcgtcgg cacctgaacg cgaggcgctc 240
cattgcgcgt gcgcgttgag gggttcccg cacctgatcg cgagacccca acggctggtg 300
gcgtcgccctg cgcgtctcgg ctgagctggc catggcgag ctgtgcgggc tgaggcggag 360
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agaacgcagc atccacgaga atgccacggg tgacctggcc accagcagga atgcagcgga 480
ttcctctgtc ccaagtgtc ccagaaggca ggattctgaa gaccactcca gcgatatgtt 540

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311

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cattgcctct tttctcatca cagaagtgat gttggaatcg tttcttttgt ttgtctgatt 1260
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tgctttcttt atgggagtc taatttcaac cctacccaaa tgatcacaag acactatctg 1440
aggtgtccca ttctagaaat agaccctca aaatagcgtc tttcagatct ttttgaatga 1500
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<210> 304

<211> 195

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(195)

<223> Xaa = Any Amino Acid

<400> 304

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Leu Gly Ser Leu Leu Leu Ser Gly Val Leu Ala Ala Asp Arg Glu Arg
          20           25           30
Ser Ile His Glu Asn Ala Thr Gly Asp Leu Ala Thr Ser Arg Asn Ala
          35           40           45
Ala Asp Ser Ser Val Pro Ser Ala Pro Arg Arg Gln Asp Ser Glu Asp
          50           55           60
His Ser Ser Asp Met Phe Asn Tyr Glu Glu Tyr Cys Thr Ala Asn Ala
65           70           75           80
Val Thr Gly Pro Cys Arg Ala Ser Phe Pro Arg Trp Tyr Phe Asp Val
          85           90           95
Glu Arg Asn Ser Cys Asn Asn Phe Ile Tyr Gly Gly Cys Arg Gly Asn
          100          105          110
Lys Asn Ser Tyr Arg Ser Glu Glu Ala Cys Met Leu Arg Cys Phe Arg
          115          120          125
Gln Gln Glu Asn Pro Pro Leu Pro Leu Gly Ser Lys Val Val Xaa Leu
          130          135          140
Ala Gly Leu Phe Val Met Val Leu Ile Leu Phe Leu Gly Ala Ser Met
145           150           155           160
Val Tyr Leu Ile Arg Val Ala Arg Arg Asn Gln Glu Arg Ala Leu Arg
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Tyr Val Leu
          195

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<210> 305

<211> 3079
 <212> DNA
 <213> Homo sapiens

<400> 305

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<210> 306
 <211> 807
 <212> PRT
 <213> Homo sapiens

<400> 306

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			20					25				30			
Thr	Leu	Asp	Lys	Val	Pro	Lys	Ser	Glu	Gly	Tyr	Cys	Ser	Arg	Ile	Leu
		35				40					45				
Arg	Ala	Gln	Gly	Thr	Arg	Arg	Glu	Gly	Tyr	Thr	Glu	Phe	Ser	Leu	Arg
	50				55						60				
Val	Glu	Gly	Asp	Pro	Asp	Phe	Tyr	Lys	Pro	Gly	Thr	Ser	Tyr	Arg	Val
65					70					75				80	
Thr	Leu	Ser	Ala	Ala	Pro	Pro	Ser	Tyr	Phe	Arg	Gly	Phe	Thr	Leu	Ile
				85					90					95	
Ala	Leu	Arg	Glu	Asn	Arg	Glu	Gly	Asp	Lys	Glu	Glu	Asp	His	Ala	Gly
			100					105					110		
Thr	Phe	Gln	Ile	Ile	Asp	Glu	Glu	Glu	Thr	Gln	Phe	Met	Ser	Asn	Cys
		115				120						125			
Pro	Val	Ala	Val	Thr	Glu	Ser	Thr	Pro	Arg	Arg	Arg	Thr	Arg	Ile	Gln
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Val	Phe	Trp	Ile	Ala	Pro	Pro	Ala	Gly	Thr	Gly	Cys	Val	Ile	Leu	Lys
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Ala	Ser	Ile	Val	Gln	Lys	Arg	Ile	Ile	Tyr	Phe	Gln	Asp	Glu	Gly	Ser
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Leu	Thr	Lys	Lys	Leu	Cys	Glu	Gln	Asp	Ser	Thr	Phe	Asp	Gly	Val	Thr
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Asp	Lys	Pro	Ile	Leu	Asp	Cys	Cys	Ala	Cys	Gly	Thr	Ala	Lys	Tyr	Arg
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Leu	Thr	Phe	Tyr	Gly	Asn	Trp	Ser	Glu	Lys	Thr	His	Pro	Lys	Asp	Tyr
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Pro	Arg	Arg	Ala	Asn	His	Trp	Ser	Ala	Ile	Ile	Gly	Gly	Ser	His	Ser
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Lys	Asn	Tyr	Val	Leu	Trp	Glu	Tyr	Gly	Gly	Tyr	Ala	Ser	Glu	Gly	Val
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Lys	Gln	Val	Ala	Glu	Leu	Gly	Ser	Pro	Val	Lys	Met	Glu	Glu	Glu	Ile
		260						265					270		
Arg	Gln	Gln	Ser	Asp	Glu	Val	Leu	Thr	Val	Ile	Lys	Ala	Lys	Ala	Gln
	275						280					285			
Trp	Pro	Ala	Trp	Gln	Pro	Leu	Asn	Val	Arg	Ala	Ala	Pro	Ser	Ala	Glu
	290					295					300				
Phe	Ser	Val	Asp	Arg	Thr	Arg	His	Leu	Met	Ser	Phe	Leu	Thr	Met	Met
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Gly	Pro	Ser	Pro	Asp	Trp	Asn	Val	Gly	Leu	Ser	Ala	Glu	Asp	Leu	Cys
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Thr	Lys	Glu	Cys	Gly	Trp	Val	Gln	Lys	Val	Val	Gln	Asp	Leu	Ile	Pro
		340					345						350		
Trp	Asp	Ala	Gly	Thr	Asp	Ser	Gly	Val	Thr	Tyr	Glu	Ser	Pro	Asn	Lys
	355					360						365			
Pro	Thr	Ile	Pro	Gln	Glu	Lys	Ile	Arg	Pro	Leu	Thr	Ser	Leu	Asp	His
	370					375					380				
Pro	Gln	Ser	Pro	Phe	Tyr	Asp	Pro	Glu	Gly	Gly	Ser	Ile	Thr	Gln	Val
385					390					395				400	
Ala	Arg	Val	Val	Ile	Glu	Arg	Ile	Ala	Arg	Lys	Gly	Glu	Gln	Cys	Asn
				405					410					415	

314

Ile	Val	Pro	Asp	Asn	Val	Asp	Asp	Ile	Val	Ala	Asp	Leu	Ala	Pro	Glu		
			420					425					430				
Glu	Lys	Asp	Glu	Asp	Asp	Thr	Pro	Glu	Thr	Cys	Ile	Tyr	Ser	Asn	Trp		
		435					440					445					
Ser	Pro	Trp	Ser	Ala	Cys	Ser	Ser	Ser	Thr	Cys	Asp	Lys	Gly	Lys	Arg		
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Met	Arg	Gln	Arg	Met	Leu	Lys	Ala	Gln	Leu	Asp	Leu	Ser	Val	Pro	Cys		
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Pro	Asp	Thr	Gln	Asp	Phe	Gln	Pro	Cys	Met	Gly	Pro	Gly	Cys	Ser	Asp		
				485					490					495			
Glu	Asp	Gly	Ser	Thr	Cys	Thr	Met	Ser	Glu	Trp	Ile	Thr	Trp	Ser	Pro		
			500					505					510				
Cys	Ser	Ile	Ser	Cys	Gly	Met	Gly	Met	Arg	Ser	Arg	Glu	Arg	Tyr	Val		
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Lys	Gln	Phe	Pro	Glu	Asp	Gly	Ser	Val	Cys	Thr	Leu	Pro	Thr	Glu	Glu		
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Met	Glu	Lys	Cys	Thr	Val	Asn	Glu	Glu	Cys	Ser	Pro	Ser	Ser	Cys	Leu		
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Met	Thr	Glu	Trp	Gly	Glu	Trp	Asp	Glu	Cys	Ser	Ala	Thr	Cys	Gly	Met		
				565					570					575			
Gly	Met	Lys	Lys	Arg	His	Arg	Met	Ile	Lys	Met	Asn	Pro	Ala	Asp	Gly		
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Ser	Met	Cys	Lys	Ala	Glu	Thr	Ser	Gln	Ala	Glu	Lys	Cys	Met	Met	Pro		
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Glu	Cys	His	Thr	Ile	Pro	Cys	Leu	Leu	Ser	Pro	Trp	Ser	Glu	Trp	Ser		
		610				615					620						
Asp	Cys	Ser	Val	Thr	Cys	Gly	Lys	Gly	Met	Arg	Thr	Arg	Gln	Arg	Met		
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Leu	Lys	Ser	Leu	Ala	Glu	Leu	Gly	Asp	Cys	Asn	Glu	Asp	Leu	Glu	Gln		
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Val	Glu	Lys	Cys	Met	Leu	Pro	Glu	Cys	Pro	Ile	Asp	Cys	Glu	Leu	Thr		
			660					665					670				
Glu	Trp	Ser	Gln	Trp	Ser	Glu	Cys	Asn	Lys	Ser	Cys	Gly	Lys	Gly	His		
		675					680					685					
Val	Ile	Arg	Thr	Arg	Met	Ile	Gln	Met	Glu	Pro	Gln	Phe	Gly	Gly	Ala		
		690				695						700					
Pro	Cys	Pro	Glu	Thr	Val	Gln	Arg	Lys	Lys	Cys	Arg	Ile	Arg	Lys	Cys		
705					710					715					720		
Leu	Arg	Asn	Pro	Ser	Ile	Gln	Lys	Pro	Arg	Trp	Arg	Glu	Ala	Arg	Glu		
			725						730					735			
Ser	Arg	Arg	Ser	Glu	Gln	Leu	Lys	Glu	Glu	Ser	Glu	Gly	Glu	Gln	Phe		
			740					745					750				
Pro	Gly	Cys	Arg	Met	Arg	Pro	Trp	Thr	Ala	Trp	Ser	Glu	Cys	Thr	Lys		
		755					760					765					
Leu	Cys	Gly	Gly	Gly	Ile	Gln	Glu	Arg	Tyr	Met	Thr	Val	Lys	Lys	Arg		
		770				775					780						
Phe	Lys	Ser	Ser	Gln	Phe	Thr	Ser	Cys	Lys	Asp	Lys	Lys	Glu	Ile	Arg		
785					790					795					800		
Ala	Cys	Asn	Val	His	Pro	Cys											
				805													

<210> 307

<211> 5108

<212> DNA

<213> Homo sapiens

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320

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<212> PRT

<213> Homo sapiens

<400> 310

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Cys Ala Gly Gly Ser Gly Gln Asn Gln Pro Ser Leu Leu Pro Leu Leu
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Arg Arg Gly Pro Pro Leu Leu Ala Leu Leu Ser Phe Ala Trp Leu Ser
50          55          60
Ser Ala Gln Leu Ser Ala Ala Pro Arg Pro Pro Ser Arg Gly Gly His
65          70          75          80
Gly Leu Arg Val Ala Asp Ala Ser Ser Glu Leu Pro Leu Ser Ala Ala
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Pro Pro Pro Gly Arg Ala Phe Val Gly Thr Thr Ser Gly Arg Ser Arg
          100          105          110
Val Ala Lys Ala Cys Gly Arg Gly Thr Lys Leu Gly Ala Ala Lys Met
          115          120          125
Arg Leu Ser Pro Ala Pro Leu Lys Leu Ser Arg Thr Pro Ala Leu Leu
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Ala Leu Ala Leu Pro Leu Ala Ala Ala Leu Ala Phe Ser Asp Glu Thr
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Leu Asp Lys Val Pro Lys Ser Glu Gly Tyr Cys Ser Arg Ile Leu Arg
          165          170          175
Ala Gln Gly Thr Arg Arg Glu Gly Tyr Thr Glu Phe Ser Leu Arg Val
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Glu Gly Asp Pro Asp Phe Tyr Lys Pro Gly Thr Ser Tyr Arg Val Thr
195          200          205
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Leu Arg Glu Asn Arg Glu Gly Asp Lys Glu Glu Asp His Ala Gly Thr
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321

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Phe	Trp	Ile	Ala	Pro	Pro	Ala	Gly	Thr	Gly	Cys	Val	Ile	Leu	Lys	Ala	275	280	285
Ser	Ile	Val	Gln	Lys	Arg	Ile	Ile	Tyr	Phe	Gln	Asp	Glu	Gly	Ser	Leu	290	295	300
Thr	Lys	Lys	Leu	Cys	Glu	Gln	Asp	Ser	Thr	Phe	Asp	Gly	Val	Thr	Asp	305	310	315
Lys	Pro	Ile	Leu	Asp	Cys	Cys	Ala	Cys	Gly	Thr	Ala	Lys	Tyr	Arg	Leu	325	330	335
Thr	Phe	Tyr	Gly	Asn	Trp	Ser	Glu	Lys	Thr	His	Pro	Lys	Asp	Tyr	Pro	340	345	350
Arg	Arg	Ala	Asn	His	Trp	Ser	Ala	Ile	Ile	Gly	Gly	Ser	His	Ser	Lys	355	360	365
Asn	Tyr	Val	Leu	Trp	Glu	Tyr	Gly	Gly	Tyr	Ala	Ser	Glu	Gly	Val	Lys	370	375	380
Gln	Val	Ala	Glu	Leu	Gly	Ser	Pro	Val	Lys	Met	Glu	Glu	Glu	Ile	Arg	385	390	395
Gln	Gln	Ser	Asp	Glu	Val	Leu	Thr	Val	Ile	Lys	Ala	Lys	Ala	Gln	Trp	405	410	415
Pro	Ala	Trp	Gln	Pro	Leu	Asn	Val	Arg	Ala	Ala	Pro	Ser	Ala	Glu	Phe	420	425	430
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Ser	Ile	Ser	Cys	Gly	Met	Gly	Met	Arg	Ser	Arg	Glu	Arg	Tyr	Val	Lys	645	650	655
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Glu	Lys	Cys	Thr	Val	Asn	Glu	Glu	Cys	Ser	Pro	Ser	Ser	Cys	Leu	Met	675	680	685
Thr	Glu	Trp	Gly	Glu	Trp	Asp	Glu	Cys	Ser	Ala	Thr	Cys	Gly	Met	Gly	690	695	700

322

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Cys	His	Thr	Ile	Pro	Cys	Leu	Leu	Ser	Pro	Trp	Ser	Glu	Trp	Ser	Asp
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Cys	Ser	Val	Thr	Cys	Gly	Lys	Gly	Met	Arg	Thr	Arg	Gln	Arg	Met	Leu
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Lys	Ser	Leu	Ala	Glu	Leu	Gly	Asp	Cys	Asn	Glu	Asp	Leu	Glu	Gln	Val
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Trp	Ser	Gln	Trp	Ser	Glu	Cys	Asn	Lys	Ser	Cys	Gly	Lys	Gly	His	Val
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<211> 782

<212> PRT

<213> Homo sapiens

<400> 312

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Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
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Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
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Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
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324

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Ile	Cys	Leu	Pro	Asp	Ala	Ser	His	Val	Phe	Pro	Ala	Gly	Lys	Ala	Ile		
		660						665					670				
Trp	Val	Thr	Gly	Trp	Gly	His	Thr	Gln	Tyr	Gly	Gly	Thr	Gly	Ala	Leu		
		675				680						685					
Ile	Leu	Gln	Lys	Gly	Glu	Ile	Arg	Val	Ile	Asn	Gln	Thr	Thr	Cys	Glu		
	690					695					700						
Asn	Leu	Leu	Pro	Gln	Gln	Ile	Thr	Pro	Arg	Met	Met	Cys	Val	Gly	Phe		

325

705					710					715				720
Leu	Ser	Gly	Gly	Val	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly	Gly	Pro
					725					730				735
Ser	Ser	Val	Glu	Ala	Asp	Gly	Arg	Ile	Phe	Gln	Ala	Gly	Val	Val
					740					745				750
Trp	Gly	Asp	Gly	Cys	Ala	Gln	Arg	Asn	Lys	Pro	Gly	Val	Tyr	Thr
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<210> 313
 <211> 2805
 <212> DNA
 <213> Homo sapiens

<400> 313

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326

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<210> 314
 <211> 323
 <212> PRT
 <213> Homo sapiens

<400> 314

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			20					25						30	
Asn	Cys	Thr	Cys	Pro	Thr	Asn	Lys	Met	Thr	Val	Cys	Ser	Pro	Asp	Gly
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Pro	Gly	Gly	Arg	Cys	Gln	Cys	Arg	Ala	Leu	Gly	Ser	Gly	Met	Ala	Val
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Asp	Cys	Ser	Thr	Leu	Thr	Ser	Lys	Cys	Leu	Leu	Leu	Lys	Ala	Arg	Met
65					70					75					80
Ser	Ala	Pro	Lys	Asn	Ala	Arg	Thr	Leu	Val	Arg	Pro	Ser	Glu	His	Ala
				85					90					95	
Leu	Val	Asp	Asn	Asp	Gly	Leu	Tyr	Asp	Pro	Asp	Cys	Asp	Pro	Glu	Gly
			100					105					110		
Arg	Phe	Lys	Ala	Arg	Gln	Cys	Asn	Gln	Thr	Ser	Val	Cys	Trp	Cys	Val
		115					120					125			
Asn	Ser	Val	Gly	Val	Arg	Arg	Thr	Asp	Lys	Gly	Asp	Leu	Ser	Leu	Arg
		130				135					140				
Cys	Asp	Glu	Leu	Val	Arg	Thr	His	His	Ile	Leu	Ile	Asp	Leu	Arg	His
145					150					155					160
Arg	Pro	Thr	Ala	Gly	Ala	Phe	Asn	His	Ser	Asp	Leu	Asp	Ala	Glu	Leu
			165					170						175	
Arg	Arg	Leu	Phe	Arg	Glu	Arg	Tyr	Arg	Leu	His	Pro	Lys	Phe	Val	Ala
			180					185					190		
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		195					200					205			
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		210				215					220				
Tyr	Phe	Glu	Arg	Asp	Ile	Lys	Gly	Glu	Ser	Leu	Phe	Gln	Gly	Arg	Gly
225				230						235					240
Gly	Leu	Asp	Leu	Arg	Val	Arg	Gly	Glu	Pro	Leu	Gln	Val	Glu	Arg	Thr
				245					250					255	
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			260					265					270		
Leu	Thr	Ala	Gly	Leu	Ile	Ala	Val	Ile	Val	Val	Val	Val	Val	Ala	Leu
		275					280					285			
Val	Ala	Gly	Met	Ala	Val	Leu	Val	Ile	Thr	Asn	Arg	Arg	Lys	Ser	Gly
		290				295					300				
Lys	Tyr	Lys	Lys	Val	Glu	Ile	Lys	Glu	Leu	Gly	Glu	Leu	Arg	Lys	Glu
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Pro	Ser	Leu													

<210> 315

327

<211> 1142

<212> DNA

<213> Homo sapiens

<400> 315

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<210> 316

<211> 235

<212> PRT

<213> Homo sapiens

<400> 316

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 20          25          30
Ala Glu Ile Cys Leu Leu Pro Leu Asp Tyr Gly Pro Cys Arg Ala Leu
 35          40          45
Leu Leu Arg Tyr Tyr Tyr Asp Arg Tyr Thr Gln Ser Cys Arg Gln Phe
 50          55          60
Leu Tyr Gly Gly Cys Glu Gly Asn Ala Asn Asn Phe Tyr Thr Trp Glu
 65          70          75          80
Ala Cys Asp Asp Ala Cys Trp Arg Ile Glu Lys Val Pro Lys Val Cys
 85          90          95
Arg Leu Gln Val Ser Val Asp Asp Gln Cys Glu Gly Ser Thr Glu Lys
100          105          110
Tyr Phe Phe Asn Leu Ser Ser Met Thr Cys Glu Lys Phe Phe Ser Gly
115          120          125
Gly Cys His Arg Asn Arg Ile Glu Asn Arg Phe Pro Asp Glu Ala Thr
130          135          140
Cys Met Gly Phe Cys Ala Pro Lys Lys Ile Pro Ser Phe Cys Tyr Ser
145          150          155          160
Pro Lys Asp Glu Gly Leu Cys Ser Ala Asn Val Thr Arg Tyr Tyr Phe
165          170          175
Asn Pro Arg Tyr Arg Thr Cys Asp Ala Phe Thr Tyr Thr Gly Cys Gly
180          185          190
Gly Asn Asp Asn Asn Phe Val Ser Arg Glu Asp Cys Lys Arg Ala Cys
195          200          205

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328

Ala Lys Ala Leu Lys Lys Lys Lys Lys Met Pro Lys Leu Arg Phe Ala
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 Ser Arg Ile Arg Lys Ile Arg Lys Lys Gln Phe
 225 230 235

<210> 317
 <211> 2307
 <212> DNA
 <213> Homo sapiens

<220>
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<400> 317
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<210> 318

<211> 428
 <212> PRT
 <213> Homo sapiens

<400> 318

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			20					25					30		
Gly	Ile	Pro	Ile	Ile	Ile	Ala	Leu	Leu	Ser	Leu	Ala	Ser	Ile	Ile	Ile
		35					40					45			
Val	Val	Val	Leu	Ile	Lys	Val	Ile	Leu	Asp	Lys	Tyr	Tyr	Phe	Leu	Cys
	50					55					60				
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65					70					75					80
Leu	Asp	Cys	Pro	Leu	Gly	Glu	Asp	Glu	Glu	His	Cys	Val	Lys	Ser	Phe
				85				90						95	
Pro	Glu	Gly	Pro	Ala	Val	Ala	Val	Arg	Leu	Ser	Lys	Asp	Arg	Ser	Thr
			100					105					110		
Leu	Gln	Val	Leu	Asp	Ser	Ala	Thr	Gly	Asn	Trp	Phe	Ser	Ala	Cys	Phe
	115						120						125		
Asp	Asn	Phe	Thr	Glu	Ala	Leu	Ala	Glu	Thr	Ala	Cys	Arg	Gln	Met	Gly
	130					135					140				
Tyr	Ser	Ser	Lys	Pro	Thr	Phe	Arg	Ala	Val	Glu	Ile	Gly	Pro	Asp	Gln
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			165					170						175	
Arg	Asn	Ser	Ser	Gly	Pro	Cys	Leu	Ser	Gly	Ser	Leu	Val	Ser	Leu	His
			180					185					190		
Cys	Leu	Ala	Cys	Gly	Lys	Ser	Leu	Lys	Thr	Pro	Arg	Val	Val	Gly	Gly
	195						200					205			
Glu	Glu	Ala	Ser	Val	Asp	Ser	Trp	Pro	Trp	Gln	Val	Ser	Ile	Gln	Tyr
	210					215					220				
Asp	Lys	Gln	His	Val	Cys	Gly	Gly	Ser	Ile	Leu	Asp	Pro	His	Trp	Val
225					230					235					240
Leu	Thr	Ala	Ala	His	Cys	Phe	Arg	Lys	His	Thr	Asp	Val	Phe	Asn	Trp
				245					250					255	
Lys	Val	Arg	Ala	Gly	Ser	Asp	Lys	Leu	Gly	Ser	Phe	Pro	Ser	Leu	Ala
			260					265					270		
Val	Ala	Lys	Ile	Ile	Ile	Ile	Glu	Phe	Asn	Pro	Met	Tyr	Pro	Lys	Asp
	275						280					285			
Asn	Asp	Ile	Ala	Leu	Met	Lys	Leu	Gln	Phe	Pro	Leu	Thr	Phe	Ser	Gly
	290					295					300				
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Ala	Thr	Pro	Leu	Trp	Ile	Ile	Gly	Trp	Gly	Phe	Thr	Lys	Gln	Asn	Gly
			325						330					335	
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			340					345					350		
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Lys	Met	Met	Cys	Ala	Gly	Ile	Pro	Glu	Gly	Gly	Val	Asp	Thr	Cys	Gln
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Gly	Asp	Ser	Gly	Gly	Pro	Leu	Met	Tyr	Gln	Ser	Asp	Gln	Trp	His	Val
385					390					395					400
Val	Gly	Ile	Val	Ser	Trp	Gly	Tyr	Gly	Cys	Gly	Gly	Pro	Ser	Thr	Pro
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420

425

<210> 319
 <211> 3529
 <212> DNA
 <213> Homo sapiens

<400> 319

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331

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<210> 320
 <211> 444
 <212> PRT
 <213> Homo sapiens

<400> 320

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Arg	Ala	Ser	Leu	Ile	Phe	Ser	Leu	Lys	Asn	Glu	Val	Gly	Gly	Leu	Ile
			20					25					30		
Lys	Ala	Leu	Lys	Ile	Phe	Gln	Glu	Lys	His	Val	Asn	Leu	Leu	His	Ile
			35				40					45			
Glu	Ser	Arg	Lys	Ser	Lys	Arg	Arg	Asn	Ser	Glu	Phe	Glu	Ile	Phe	Val
			50			55					60				
Asp	Cys	Asp	Ile	Asn	Arg	Glu	Gln	Leu	Asn	Asp	Ile	Phe	His	Leu	Leu
65				70					75					80	
Lys	Ser	His	Thr	Asn	Val	Leu	Ser	Val	Asn	Leu	Pro	Asp	Asn	Phe	Thr
			85						90					95	
Leu	Lys	Glu	Asp	Gly	Met	Glu	Thr	Val	Pro	Trp	Phe	Pro	Lys	Lys	Ile
			100					105					110		
Ser	Asp	Leu	Asp	His	Cys	Ala	Asn	Arg	Val	Leu	Met	Tyr	Gly	Ser	Glu
			115				120					125			
Leu	Asp	Ala	Asp	His	Pro	Gly	Phe	Lys	Asp	Asn	Val	Tyr	Arg	Lys	Arg
			130			135					140				
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145				150						155					160
Ile	Pro	Lys	Val	Glu	Phe	Thr	Glu	Glu	Glu	Ile	Lys	Thr	Trp	Gly	Thr
			165						170					175	
Val	Phe	Gln	Glu	Leu	Asn	Lys	Leu	Tyr	Pro	Thr	His	Ala	Cys	Arg	Glu
			180					185					190		
Tyr	Leu	Lys	Asn	Leu	Pro	Leu	Leu	Ser	Lys	Tyr	Cys	Gly	Tyr	Arg	Glu
			195			200						205			
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			210			215					220				
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Phe	Leu	Ser	Gly	Leu	Ala	Phe	Arg	Val	Phe	His	Cys	Thr	Gln	Tyr	Val
			245						250					255	
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Glu	Leu	Leu	Gly	His	Val	Pro	Leu	Leu	Ala	Glu	Pro	Ser	Phe	Ala	Gln
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Phe	Ser	Gln	Glu	Ile	Gly	Leu	Ala	Ser	Leu	Gly	Ala	Ser	Glu	Glu	Ala
			290			295					300				
Val	Gln	Lys	Leu	Ala	Thr	Cys	Tyr	Phe	Phe	Thr	Val	Glu	Phe	Gly	Leu
305				310						315					320
Cys	Lys	Gln	Asp	Gly	Gln	Leu	Arg	Val	Phe	Gly	Ala	Gly	Leu	Leu	Ser

332

			325					330				335			
Ser	Ile	Ser	Glu	Leu	Lys	His	Ala	Leu	Ser	Gly	His	Ala	Lys	Val	Lys
			340					345					350		
Pro	Phe	Asp	Pro	Lys	Ile	Thr	Cys	Lys	Gln	Glu	Cys	Leu	Ile	Thr	Thr
		355					360					365			
Phe	Gln	Asp	Val	Tyr	Phe	Val	Ser	Glu	Ser	Phe	Glu	Asp	Ala	Lys	Glu
	370					375					380				
Lys	Met	Arg	Glu	Phe	Thr	Lys	Thr	Ile	Lys	Arg	Pro	Phe	Gly	Val	Lys
385					390				395					400	
Tyr	Asn	Pro	Tyr	Thr	Arg	Ser	Ile	Gln	Ile	Leu	Lys	Asp	Thr	Lys	Ser
			405					410					415		
Ile	Thr	Ser	Ala	Met	Asn	Glu	Leu	Gln	His	Asp	Leu	Asp	Val	Val	Ser
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Asp	Ala	Leu	Ala	Lys	Val	Ser	Arg	Lys	Pro	Ser	Ile				
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<210> 321

<211> 3505

<212> DNA

<213> Homo sapiens

<400> 321

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gagatttttg ttgactgtga catcaacaga gaacaattga atgatatttt tcatctgtctg 240
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333

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<210> 322

<211> 466

<212> PRT

<213> Homo sapiens

<400> 322

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Lys Ala Leu Lys Ile Phe Gln Glu Lys His Val Asn Leu Leu His Ile
 35           40           45
Glu Ser Arg Lys Ser Lys Arg Arg Asn Ser Glu Phe Glu Ile Phe Val
 50           55           60
Asp Cys Asp Ile Asn Arg Glu Gln Leu Asn Asp Ile Phe His Leu Leu
 65           70           75           80
Lys Ser His Thr Asn Val Leu Ser Val Asn Leu Pro Asp Asn Phe Thr
 85           90           95
Leu Lys Glu Asp Gly Met Glu Thr Val Pro Trp Phe Pro Lys Lys Ile
100          105          110
Ser Asp Leu Asp His Cys Ala Asn Arg Val Leu Met Tyr Gly Ser Glu
115          120          125
Leu Asp Ala Asp His Pro Gly Phe Lys Asp Asn Val Tyr Arg Lys Arg
130          135          140
Arg Lys Tyr Phe Ala Asp Leu Ala Met Asn Tyr Lys His Gly Asp Pro
145          150          155          160
Ile Pro Lys Val Glu Phe Thr Glu Glu Glu Ile Lys Thr Trp Gly Thr
165          170          175
Val Phe Gln Glu Leu Asn Lys Leu Tyr Pro Thr His Ala Cys Arg Glu
180          185          190
Tyr Leu Lys Asn Leu Pro Leu Leu Ser Lys Tyr Cys Gly Tyr Arg Glu
195          200          205
Asp Asn Ile Pro Gln Leu Glu Asp Val Ser Asn Phe Leu Lys Glu Arg

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334

210	215	220
Thr Gly Phe Ser Ile Arg	Pro Val Ala Gly Tyr	Leu Ser Pro Arg Asp
225	230	235
Phe Leu Ser Gly Leu Ala	Phe Arg Val Phe His	Cys Thr Gln Tyr Val
245	250	255
Arg His Ser Ser Asp Pro	Phe Tyr Thr Pro Glu	Pro Asp Thr Cys His
260	265	270
Glu Leu Leu Gly His Val	Pro Leu Leu Ala Glu	Pro Ser Phe Ala Gln
275	280	285
Phe Ser Gln Glu Ile Gly	Leu Ala Ser Leu Gly	Ala Ser Glu Glu Ala
290	295	300
Val Gln Lys Leu Ala Thr	Cys Tyr Phe Phe Thr	Val Glu Phe Gly Leu
305	310	315
Cys Lys Gln Asp Gly Gln	Leu Arg Val Phe Gly	Ala Gly Leu Leu Ser
325	330	335
Ser Ile Ser Glu Leu Lys	His Ala Leu Ser Gly	His Ala Lys Val Lys
340	345	350
Pro Phe Asp Pro Lys Ile	Thr Cys Lys Gln Glu	Cys Leu Ile Thr Thr
355	360	365
Phe Gln Asp Val Tyr Phe	Val Ser Glu Ser Phe	Glu Asp Ala Lys Glu
370	375	380
Lys Met Arg Glu Phe Thr	Lys Thr Ile Lys Arg	Pro Phe Gly Val Lys
385	390	395
Tyr Asn Pro Tyr Thr Arg	Ser Ile Gln Ile Leu	Lys Asp Thr Lys Ser
405	410	415
Ile Thr Ser Ala Met Asn	Glu Leu Gln His Asp	Leu Asp Val Val Ser
420	425	430
Asp Ala Leu Ala Lys Ser	Leu Asn Glu Asp Val	Leu Gln Val Ser Val
435	440	445
Phe Ala Leu Leu Leu Phe	Leu Pro Ser Leu His	Gly Glu Cys His Pro
450	455	460
Asp Thr		
465		

<210> 323

<211> 1154

<212> DNA

<213> Homo sapiens

<400> 323

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335

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<210> 324
<211> 258
<212> PRT
<213> Homo sapiens

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<400> 324
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Leu Ile Phe Leu Cys Gly Ala Ala Leu Leu Ala Val Gly Ile Trp Val
          20           25           30
Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser
          35           40           45
Ser Ala Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly
          50           55           60
Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr
          65           70           75           80
Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Leu Ile
          85           90           95
Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr
          100          105          110
Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys
          115          120          125
Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
          130          135          140
Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
          145          150          155          160
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
          165          170          175
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
          180          185          190
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
          195          200          205
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
          210          215          220
Leu Glu Phe Phe Ser Asn Ser Ala Arg Arg Pro Pro Leu Pro Glu Ser
          225          230          235          240
Leu Tyr Ser Thr Pro Ile Arg Arg Asp His Val Phe Leu Gln Pro Ser
          245          250          255
Pro Pro

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<210> 325
<211> 1076
<212> DNA
<213> Homo sapiens

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<400> 325
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336

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<210> 326

<211> 241

<212> PRT

<213> Homo sapiens

<400> 326

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Met Gln Cys Phe Ser Phe Ile Lys Thr Met Met Ile Leu Phe Asn Leu
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      20             25             30
Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser
      35             40             45
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Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr
      65             70             75             80
Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Leu Ile
      85             90             95
Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr
      100            105            110
Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys
      115            120            125
Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
      130            135            140
Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
      145            150            155            160
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
      165            170            175
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Glu Gln Lys Ala
      180            185            190
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
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<210> 327

<211> 2244

<212> DNA

<213> Homo sapiens

<400> 327

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<210> 328

<211> 498

<212> PRT

<213> Homo sapiens

<400> 328

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Ser Gln Thr Lys Gln Ser Ser Ile Ile Ile Gln Pro Arg Gln Cys Thr
35           40           45
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Pro Gly Gln Arg Val Thr Thr Thr Tyr Asn Gln Ser Pro Ala Ser Phe
85           90           95

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338

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 Leu Glu Arg Lys Leu Lys Cys Lys Asp Thr Leu Leu His Asn Gly Asn
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<210> 329

<211> 3649

<212> DNA

<213> Homo sapiens

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340

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 <212> PRT
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<400> 330

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341

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342

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 cacagtggctc tgggcatccc aagttgacca gggagccaac ttctcggaag tctccaatac 660
 cagctttgag ctgaactctg agaatgtgac catgaagggt gtgtctgtgc tctacaatgt 720
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<210> 332
 <211> 282
 <212> PRT
 <213> Homo sapiens

<400> 332
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 20 25 30
 Gly Arg His Ser Ile Thr Val Thr Thr Val Ala Ser Ala Gly Asn Ile
 35 40 45
 Gly Glu Asp Gly Ile Gln Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu
 50 55 60
 Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val
 65 70 75 80
 His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met
 85 90 95
 Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn
 100 105 110

343

Ala Ser Leu Arg Leu Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr
 115 120 125
 Lys Cys Tyr Ile Ile Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu
 130 135 140
 Tyr Lys Thr Gly Ala Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn
 145 150 155 160
 Ala Ser Ser Glu Thr Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln
 165 170 175
 Pro Thr Val Val Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser
 180 185 190
 Glu Val Ser Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met
 195 200 205
 Lys Val Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser
 210 215 220
 Cys Met Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val
 225 230 235 240
 Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser
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 Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu
 260 265 270
 Leu Pro Leu Ser Pro Tyr Leu Met Leu Lys
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<210> 333
 <211> 1984
 <212> DNA
 <213> Homo sapiens

<400> 333
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 aagttggtat gtggcttcat tctggaacct cggctgttga ttcaacagag aaagggacag 300
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 aaggtgcttt gtgctaagga tgaagataca attcctcagc tcttggtaga cttttgggaa 480
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 tcacagtaca tctggagatt gtctaagagg cagcctcctg acaccacacc attgogaaca 600
 tcggaggatc tgataaatgc ctgtagtcat tatggcttaa tttatccatg ggttcatgtc 660
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344

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tagaagtttta caaagctaac tttcttcttg tctagctatt aacatgattt gtcaaatagca 1860
tggtttttttc agccaaagcc ttgttttccat ttttgttgat gtgtactctt gctctttttag 1920
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aaaa                                              1984

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<210> 334
 <211> 258
 <212> PRT
 <213> Homo sapiens

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<400> 334
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 20          25          30
Lys Leu Asp Thr Ser Gly Phe Ser Ile Leu Val Thr Leu Thr Lys
 35          40          45
Ala Ala Val Ala Leu Lys Met Gly Asp Leu Asp Met His Arg Asn Glu
 50          55          60
Met Lys Ser His Ser Glu Met Lys Leu Val Cys Gly Phe Ile Leu Glu
 65          70          75          80
Pro Arg Leu Leu Ile Gln Gln Arg Lys Gly Gln Ile Val Pro Thr Glu
 85          90          95
Leu Ala Leu His Leu Lys Glu Thr Gln Pro Gly Leu Leu Val Ala Ser
100          105          110
Val Leu Gly Leu Gln Lys Asn Asn Lys Ile Gly Ile Glu Glu Ala Asp
115          120          125
Ser Phe Phe Lys Val Leu Cys Ala Lys Asp Glu Asp Thr Ile Pro Gln
130          135          140
Leu Leu Val Asp Phe Trp Glu Ala Gln Leu Val Ala Cys Leu Pro Asp
145          150          155          160
Val Val Leu Gln Glu Leu Phe Phe Lys Leu Thr Ser Gln Tyr Ile Trp
165          170          175
Arg Leu Ser Lys Arg Gln Pro Pro Asp Thr Thr Pro Leu Arg Thr Ser
180          185          190
Glu Asp Leu Ile Asn Ala Cys Ser His Tyr Gly Leu Ile Tyr Pro Trp
195          200          205
Val His Val Val Ile Ser Ser Asp Ser Leu Ala Asp Lys Asn Tyr Thr
210          215          220
Glu Asp Leu Ser Lys Leu Gln Leu Pro Leu Phe Arg Ser Trp Ser His
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Phe Gln Lys Thr Leu Leu Pro Ala Ser Val Ser Met Phe Cys Val Val
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His Ala

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<210> 335
 <211> 2180
 <212> DNA
 <213> Homo sapiens

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 <223> n = A,T,C or G

<400> 335

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cgggctcagg tctgtcggct tcccagcgtc gggcggagct gcgtcggaga aagctgctca 180
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ttaaaccacc tgagtgcagt agtgatgtca acctgagct ccggcagcgg aacagagggg 480
acctgacagc ggactcggtc cagaggggtt ccgccatgg cctagagcag tacctttcca 540
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ttcttgctct tggagtcaga gcttttggtt gcaaatactt gtccatattt gctccatttc 720
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cacctggcct tataaatatc cttttaacta actcagtaac tgccatattt tgttggttg 2040
tcttcttaaa agaataataa actaaagtgt taatgtcact tgggtgttaca tttccttaca 2100
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<210> 336

<211> 234

<212> PRT

<213> Homo sapiens

<400> 336

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      20             25             30
Arg Arg Lys Leu Leu Met Asn Ser Glu Gln Arg Ile Asn Arg Ile Met
      35             40             45
Gly Phe His Arg Pro Gly Ser Gly Ala Glu Glu Glu Ser Gln Thr Lys
      50             55             60
Ser Lys Gln Gln Asp Ser Asp Lys Leu Asn Ser Leu Ser Val Pro Ser
      65             70             75             80
Val Ser Lys Arg Val Val Leu Gly Asp Ser Val Ser Thr Gly Thr Thr
      85             90             95

```

346

Asp	Gln	Gln	Gly	Gly	Val	Ala	Glu	Val	Lys	Gly	Thr	Gln	Leu	Gly	Asp
			100					105					110		
Lys	Leu	Asp	Ser	Phe	Ile	Lys	Pro	Pro	Glu	Cys	Ser	Ser	Asp	Val	Asn
		115					120					125			
Leu	Glu	Leu	Arg	Gln	Arg	Asn	Arg	Gly	Asp	Leu	Thr	Ala	Asp	Ser	Val
	130					135					140				
Gln	Arg	Gly	Ser	Arg	His	Gly	Leu	Glu	Gln	Tyr	Leu	Ser	Arg	Phe	Glu
145					150					155					160
Glu	Ala	Met	Lys	Leu	Arg	Lys	Gln	Leu	Ile	Ser	Glu	Lys	Pro	Ser	Gln
			165						170					175	
Glu	Asp	Gly	Asn	Thr	Thr	Glu	Glu	Phe	Asp	Ser	Phe	Arg	Ile	Phe	Arg
			180					185					190		
Leu	Val	Gly	Cys	Ala	Leu	Leu	Ala	Leu	Gly	Val	Arg	Ala	Phe	Val	Cys
	195						200					205			
Lys	Tyr	Leu	Ser	Ile	Phe	Ala	Pro	Phe	Leu	Thr	Leu	Gln	Leu	Ala	Leu
	210					215					220				
His	Gly	Ile	Ile	Gln	Ile	Phe	Ser	Gln	Glu						
225					230										

<210> 337
 <211> 3695
 <212> DNA
 <213> Homo sapiens

<400> 337

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ccgtcgcgct	cgaccccgag	ggcatgcggc	agccgcaggg	gccccgcgtc	ccgggctcgg	180
cggcgcgggt	gaacgtgagc	ggatgttcac	ttcttctcca	caatgaatga	gtgtcactat	240
gacaagcaca	tggacttttt	ttataatagg	agcaacactg	atactgtcga	tgactggaca	300
ggaacaaagc	ttgtgattgt	tttgtgtgtt	gggacgtttt	tctgcctgtt	tatttttttt	360
tctaattctc	tggtcatcgc	ggcagtgatc	aaaaacagaa	aatttcattt	ccccttctac	420
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347

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tatatatata tatatatata tattcctgatt ttatttgatt ttgttcaaag 2040
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<210> 338

<211> 353

<212> PRT

<213> Homo sapiens

<400> 338

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Ser Asn Thr Asp Thr Val Asp Asp Trp Thr Gly Thr Lys Leu Val Ile
             20             25             30
Val Leu Cys Val Gly Thr Phe Phe Cys Leu Phe Ile Phe Phe Ser Asn
             35             40             45
Ser Leu Val Ile Ala Ala Val Ile Lys Asn Arg Lys Phe His Phe Pro
             50             55             60
Phe Tyr Tyr Leu Leu Ala Asn Leu Ala Ala Asp Phe Phe Ala Gly
65             70             75             80
Ile Ala Tyr Val Phe Leu Met Phe Asn Thr Gly Pro Val Ser Lys Thr
             85             90             95
Leu Thr Val Asn Arg Trp Phe Leu Arg Gln Gly Leu Leu Asp Ser Ser
             100            105            110
Leu Thr Ala Ser Leu Thr Asn Leu Leu Val Ile Ala Val Glu Arg His
             115            120            125
Met Ser Ile Met Arg Met Arg Val His Ser Asn Leu Thr Lys Lys Arg
             130            135            140
Val Thr Leu Leu Ile Leu Leu Val Trp Ala Ile Ala Ile Phe Met Gly
145            150            155            160
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[illegible]

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<210> 339
<211> 3320
<212> DNA
<213> Homo sapiens
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aacttcggga	aggcggtgat	ccagctcacc	accaagacgc	agcccggtga	agccaccgat	180	
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349

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<210> 340

<211> 784

<212> PRT

<213> Homo sapiens

<400> 340

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             50             55             60
Asn Leu Ala Thr Leu Cys Tyr Lys Ala Val Glu Lys Leu Val Gln Gly
65             70             75             80
Ala Glu Ser Gly Cys His Ser Glu Lys Glu Lys Gln Ile Val Leu Asn
             85             90             95
Cys Ser Arg Leu Leu Thr Arg Val Leu Pro Tyr Ile Phe Glu Asp Pro
             100            105            110
Asp Trp Arg Gly Phe Phe Trp Ser Thr Val Pro Gly Ala Gly Arg Gly
             115            120            125
Gly Gln Gly Glu Glu Asp Asp Glu His Ala Arg Pro Leu Ala Glu Ser
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Leu Leu Leu Ala Ile Ala Asp Leu Leu Phe Cys Pro Asp Thr Gln Ser
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350

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Gln	Pro	Asn	Tyr	Ile	His	Asp	Met	Asn	Arg	Met	Glu	Leu	Leu	Lys	Leu		
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351

Lys	Ser	Gln	Val	Ser	Glu	Asp	Gly	Thr	Leu	Arg	Ser	Leu	Glu	Pro	Glu
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<211> 3307

<212> DNA

<213> Homo sapiens

<400> 341

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<210> 342

<211> 788

<212> PRT

<213> Homo sapiens

<400> 342

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 50           55           60
Asn Leu Ala Thr Leu Cys Tyr Lys Ala Val Glu Lys Leu Val Gln Gly
 65           70           75           80
Ala Glu Ser Gly Cys His Ser Glu Lys Glu Lys Gln Ile Val Leu Asn
 85           90           95
Cys Ser Arg Leu Leu Thr Arg Val Leu Pro Tyr Ile Phe Glu Asp Pro
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Asp Trp Arg Gly Phe Phe Trp Ser Thr Val Pro Gly Ala Gly Arg Gly
 115          120          125
Gly Gln Gly Glu Glu Asp Asp Glu His Ala Arg Pro Leu Ala Glu Ser
 130          135          140
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Gln Ser His Arg Arg Ser Thr Val Asp Ser Ala Glu Asp Val His Ser
 165          170          175
Leu Asp Ser Cys Glu Tyr Ile Trp Glu Ala Gly Val Gly Phe Ala His
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353

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Cys	Ala	Tyr	Asp	Pro	Val	Gly	Tyr	Gly	Ile	Pro	Tyr	Asn	His	Leu	Leu
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Phe	Ser	Asp	Tyr	Arg	Glu	Pro	Leu	Val	Glu	Glu	Ala	Ala	Gln	Val	Leu
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Ile	Val	Thr	Leu	Asp	His	Asp	Ser	Ala	Ser	Ser	Ala	Ser	Pro	Thr	Val
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Glu	Pro	Gly	Thr	Leu	Lys	Thr	Ser	Leu	Val	Ala	Thr	Pro	Gly	Ile	Asp
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Lys	Leu	Thr	Glu	Lys	Ser	Gln	Val	Ser	Glu	Asp	Gly	Thr	Leu	Arg	Ser
625					630					635					640
Leu	Glu	Pro	Glu	Pro	Gln	Gln	Ser	Leu	Glu	Asp	Gly	Ser	Pro	Ala	Lys
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Gly	Glu	Pro	Ser	Gln	Ala	Trp	Arg	Glu	Gln	Arg	Arg	Pro	Ser	Thr	Ser

355

<210> 345
 <211> 3733
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(3733)
 <223> n = A,T,C or G

<400> 345
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 cagacacctc atagcaacct atttatacaa aggggggaaag aaacacctga gcagaatgga 180
 atcattatatt ttttcccaag gagaaaaccg gggtaaaggg aggggaagcaa ttcaatttgg 240
 agtccctgtg aatgggcttt cagaaggcaa ttaaagaaat ccactcagag aggacttggg 300
 gtgaaacttg ggtcctgtgg ttttctgatt gtaagtggaa gcaggctctg cacacgctgt 360
 tggcaaagtgt caggaccagg ttaagtgaact ggagaaaaa cttccagggtg gaacaagcaa 420
 cccaggttct gctgcaagct tgaaggagcc tggagcggga gaaagctaac ttgaacatga 480
 cctgttgcat ttggcaagtt ctagcaacat gctcctaagg aagcgataca ggcacagacc 540
 atgcagactc cagttcctcc tgctgctcct gatgctggga tgcgtcctga tgatgggtggc 600
 gatgttgac cctccccacc acacctgca ccagactgtc acagcccaag ccagcaagca 660
 cagccctgaa gccagggtacc gcctggactt tggggaatcc caggattggg tactggaagc 720
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 gttcagcctg gaccacagtg gcctccagga ggactcagt gcccgcattc ccctccagag 1020
 ggctctgccc gaggtgcggc accactgtg tctgcagcag caccctcagg acagcctgcc 1080
 cacagccagc gtcactcctc gtttccatga tgagycctgg tccactctcc tgcggactgt 1140
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 ggtgttgagc tggaagctgg atttccactg ggaacctttg ccagagcatg tgaggaagc 1560
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 caataaagat ttgtacctgc gtccgtgtga tggaaaagcc cgcagcagc ggcgatttga 2400
 ccagataaat gctgtgggat aacgatgaat gtcaatgtca gaaggaaaag agaatttttg 2460
 ccatcaaaat ccagctccaa gtgaacttaa agagcttata tatttcatga agctgatcct 2520
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 tctttgtttt tctccactga gcacttaaca attgnccttc tctctggcct ggacattctc 2760
 tggcagcacc tccaggatac ataaattcaa tggatcaatt tatttgtctt caaatggcct 2820

356

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taacttggat tgtctgtttg gccaacatg aaaattaaag agtgtaagca gatgtaatgg 2880
cctgacattc caaaaactct gaattgggtt tattagcaca aatgttgtgt tcatttgttg 2940
agccatatct cagaangaag gaaanggna gctacagaaa nggaggttta ggattgcaga 3000
gaangatgca agnagcactt tggccaatt ctcnagctn caaccagca gctgaaaagc 3060
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agtaccagca caatttgagc attcccatga acaaagggtg tcacagttga gaaactctcc 3300
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gctgaggcaa gagaatcgct tgaaccatg angcagaagg tgcaatnagc tganatcatg 3540
ccattgcact tcaacctggg ngacagagtg ggactncatc tcaaaaaaaaa aaaaaagagg 3600
gaacctttct gggncctgtg tacagggttg cactgctgga gcanaacaca cttttttnaa 3660
aaagcaaacc tttttctggg gaggnaaagc caaaactggn ccaaantttt tgacnggaaa 3720
atttgggggt aag 3733

```

<210> 346

<211> 639

<212> PRT

<213> Homo sapiens

<400> 346

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 1             5             10             15
Leu Leu Leu Leu Leu Met Leu Gly Cys Val Leu Met Met Val Ala Met
 20             25             30
Leu His Pro Pro His His Thr Leu His Gln Thr Val Thr Ala Gln Ala
 35             40             45
Ser Lys His Ser Pro Glu Ala Arg Tyr Arg Leu Asp Phe Gly Glu Ser
 50             55             60
Gln Asp Trp Val Leu Glu Ala Glu Asp Glu Gly Glu Glu Tyr Ser Pro
 65             70             75             80
Leu Glu Gly Leu Pro Phe Ile Ser Leu Arg Glu Asp Gln Leu Leu
 85             90             95
Val Ala Val Ala Leu Pro Gln Ala Arg Arg Asn Gln Ser Gln Gly Arg
100            105            110
Arg Gly Gly Ser Tyr Arg Leu Ile Lys Gln Pro Arg Arg Gln Asp Lys
115            120            125
Glu Ala Pro Lys Arg Asp Trp Gly Ala Asp Glu Asp Gly Glu Val Ser
130            135            140
Glu Glu Glu Glu Leu Thr Pro Phe Ser Leu Asp Pro Arg Gly Leu Gln
145            150            155            160
Glu Ala Leu Ser Ala Arg Ile Pro Leu Arg Arg Ala Leu Pro Glu Val
165            170            175
Arg His Pro Leu Cys Leu Gln Gln His Pro Gln Asp Ser Leu Pro Thr
180            185            190
Ala Ser Val Ile Leu Cys Phe His Asp Glu Ala Trp Ser Thr Leu Leu
195            200            205
Arg Thr Val His Ser Ile Leu Asp Thr Val Pro Arg Ala Phe Leu Lys
210            215            220
Glu Ile Ile Leu Val Asp Asp Leu Ser Gln Gln Gly Gln Leu Lys Ser
225            230            235            240
Ala Leu Ser Glu Tyr Val Ala Arg Leu Glu Gly Val Lys Leu Leu Arg
245            250            255
Ser Asn Lys Arg Leu Gly Ala Ile Arg Ala Arg Met Leu Gly Ala Thr
260            265            270
Arg Ala Thr Gly Asp Val Leu Val Phe Met Asp Ala His Cys Glu Cys

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357

275	280	285
His Pro Gly Trp Leu Glu Pro Leu Leu Ser Arg Ile Ala Gly Asp Arg		
290	295	300
Ser Arg Val Val Ser Pro Val Ile Asp Val Ile Asp Trp Lys Thr Phe		
305	310	315
Gln Tyr Tyr Pro Ser Lys Asp Leu Gln Arg Gly Val Leu Asp Trp Lys		
325	330	335
Leu Asp Phe His Trp Glu Pro Leu Pro Glu His Val Arg Lys Ala Leu		
340	345	350
Gln Ser Pro Ile Ser Pro Ile Arg Ser Pro Val Val Pro Gly Glu Val		
355	360	365
Val Ala Met Asp Arg His Tyr Phe Gln Asn Thr Gly Ala Tyr Asp Ser		
370	375	380
Leu Met Ser Leu Arg Gly Gly Glu Asn Leu Glu Leu Ser Phe Lys Ala		
385	390	395
Trp Leu Cys Gly Gly Ser Val Glu Ile Leu Pro Cys Ser Arg Val Gly		
405	410	415
His Ile Tyr Gln Asn Gln Asp Ser His Ser Pro Leu Asp Gln Glu Ala		
420	425	430
Thr Leu Arg Asn Arg Val Arg Ile Ala Glu Thr Trp Leu Gly Ser Phe		
435	440	445
Lys Glu Thr Phe Tyr Lys His Ser Pro Glu Ala Phe Ser Leu Ser Lys		
450	455	460
Ala Glu Lys Pro Asp Cys Met Glu Arg Leu Gln Leu Gln Arg Arg Leu		
465	470	475
Gly Cys Arg Thr Phe His Trp Phe Leu Ala Asn Val Tyr Pro Glu Leu		
485	490	495
Tyr Pro Ser Glu Pro Arg Pro Ser Phe Ser Gly Lys Leu His Asn Thr		
500	505	510
Gly Leu Gly Leu Cys Ala Asp Cys Gln Ala Glu Gly Asp Ile Leu Gly		
515	520	525
Cys Pro Met Val Leu Ala Pro Cys Ser Asp Ser Arg Gln Gln Gln Tyr		
530	535	540
Leu Gln His Thr Ser Arg Lys Glu Ile His Phe Gly Ser Pro Gln His		
545	550	555
Leu Cys Phe Ala Val Arg Gln Glu Gln Val Ile Leu Gln Asn Cys Thr		
565	570	575
Glu Glu Gly Leu Ala Ile His Gln Gln His Trp Asp Phe Gln Glu Asn		
580	585	590
Gly Met Ile Val His Ile Leu Ser Gly Lys Cys Met Glu Ala Val Val		
595	600	605
Gln Glu Asn Asn Lys Asp Leu Tyr Leu Arg Pro Cys Asp Gly Lys Ala		
610	615	620
Arg Gln Gln Trp Arg Phe Asp Gln Ile Asn Ala Val Asp Glu Arg		
625	630	635

<210> 347

<211> 1891

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(1891)

<223> n = A,T,C or G

<400> 347

358

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tattctggct ggagcaattg cactcatcat tggctttggt atttcagggg gacactccat 180
cacagtcact actgtcgoot cagctgggaa cattggggag gatggaatcc tgagctgcac 240
ttttgaacct gacatcaaac tttctgatat cgtgatacaa tggctgaagg aagggtgttt 300
aggcttggtc catgagttca aagaaggcaa agatgagctg tcggagcagg atgaaatgtt 360
cagaggccgg acagcagtggt ttgctgatca agtgatagtt ggcaatgcct ctttgcggct 420
gaaaaacgtg caactcacag atgctggcac ctacaaatgt tatatcatca cttctaaagg 480
caaggggaat gctaaccttg agtataaaaac tggagccttc agcatgccgg aagtgaatgt 540
ggactataat gccagctcag agaccttgcg gtgtgaggct ccccgatggt tccccagcc 600
cacagtggct tgggcatccc aagttgacca gggagccaac ttctoggaag tctccaatc 660
cagcttttag ctgaactctg agaatgtgac catgaagggt gtgtctgtgc tctaccaatg 720
taogatcaac aacacatact cctgtatgat tgaaaatgac attgccaaag caacagggga 780
tatcaaagtg acagaatcgg agatcaaaaag gcggagtcac ctacagctgc taaactcaaa 840
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acagggatct acagaactat ttcaccacca gatatgacct agttttatat ttctgggagg 1020
aaatgaattc atatctagaa gtctggagtg agcaaacaag agcaagaaac aaaaagaagc 1080
caaaagcaga wrkctscarw atkmcccctt agcgtggtcg cssccssagg tacaggacgt 1140
ctcccatta caactacca atccgaagtg tcaactgtgt caggactaag aaaccctggt 1200
tttgagttag aaagggcctg gaaagagggg agccaacaaa tctgtctgct tctcacatt 1260
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cctgcaagcc aagttctgta agagaaatgc ctgagttcta gctcagggtt tcttactctg 1500
aathtagatc tccagaccct tcctggccac aattcaaatt aaggcaacaa acatatacct 1560
tccatgaang cacacacaga cttttgaaag caaggacaat gactgcttga attgaggcct 1620
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acactncttc atgtgttaan ccactgcnc tncctggann ccttggnang ccacggntg 1740
nactgntatt nacatngttg ttnnatagaa aanncntgat tttaganngt tnctgnatcg 1800
nttcaagna gaatgnattw aaaatatacy attttccbaa aaaaaaaaaa aaaaaaaaaa 1860
maaagtacct cggccgcgac cacgctaagg g 1891

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<210> 348

<211> 282

<212> PRT

<213> Homo sapiens

<400> 348

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Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile
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Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser
          20          25          30
Gly Arg His Ser Ile Thr Val Thr Val Ala Ser Ala Gly Asn Ile
          35          40          45
Gly Glu Asp Gly Ile Leu Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu
          50          55          60
Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val
          65          70          75          80
His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met
          85          90          95
Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn
          100         105         110
Ala Ser Leu Arg Leu Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr
          115         120         125
Lys Cys Tyr Ile Ile Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu
          130         135         140
Tyr Lys Thr Gly Ala Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn

```


359

145		150		155		160
Ala Ser Ser Glu Thr	Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln					
	165		170			175
Pro Thr Val Val Trp	Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser					
	180		185			190
Glu Val Ser Asn Thr	Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met					
	195		200			205
Lys Val Val Ser Val	Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser					
	210		215			220
Cys Met Ile Glu Asn	Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val					
	225		230			235
Thr Glu Ser Glu Ile	Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser					
	245		250			255
Lys Ala Ser Leu Cys	Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu					
	260		265			270
Leu Pro Leu Ser Pro	Tyr Leu Met Leu Lys					
	275		280			

<210> 349

<211> 1517

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(1517)

<223> n = A,T,C or G

<400> 349

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ttgggagtc atagctaagc accaggagct gagcactgcc cgctgtgcct gcctgcaagt 240
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caatgcagat aagccaatca tgggatgaga gcttgagcct gagtgcagct gattttgaca 540
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caccaccag gggattcgga aagatgttcg tgagcagcag tggattgcca ccaagtccag 660
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gttcatgttc agatatattt gatggcagta gtagcagcag tggcttatcc tcagaccgcg 900
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gattaaagtt ttacagattt cacacattct gatgctatta ttaactcttg gcatctctct 1140
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<210> 350

360

<211> 243
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> VARIANT
 <222> (1)...(243)
 <223> Xaa = Any Amino Acid

<400> 350
 Met Ala Gln Glu Lys Met Glu Leu Asp Leu Glu Pro Asp Thr Ser Tyr
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 Gly Gly Thr Leu Arg Arg Ser Ser Ser Ala Pro Leu Ile His Gly Leu
 20 25 30
 Ser Asp Leu Ser Gln Val Phe Gln Pro Tyr Thr Leu Arg Thr Arg Arg
 35 40 45
 Asn Ser Thr Thr Ile Met Ser Arg His Ser Leu Glu Glu Gly Leu Asp
 50 55 60
 Met Val Asn Arg Glu Thr Ala His Glu Arg Glu Met Gln Thr Ala Met
 65 70 75 80
 Gln Ile Ser Gln Ser Trp Asp Glu Ser Leu Ser Leu Ser Asp Ser Asp
 85 90 95
 Phe Asp Lys Pro Glu Lys Leu Tyr Ser Pro Lys Arg Ile Asp Phe Thr
 100 105 110
 Pro Val Ser Pro Ala Pro Ser Pro Thr Arg Gly Phe Gly Lys Met Phe
 115 120 125
 Val Ser Ser Ser Gly Leu Pro Pro Ser Pro Val Pro Ser Pro Arg Arg
 130 135 140
 Phe Ser Ser Arg Arg Ser Gln Ser Pro Val Lys Cys Ile Arg Pro Ser
 145 150 155 160
 Val Leu Gly Pro Leu Lys Arg Lys Gly Glu Met Glu Thr Glu Ser Gln
 165 170 175
 Pro Lys Arg Leu Phe Gln Gly Thr Thr Asn Met Leu Ser Pro Asp Ala
 180 185 190
 Ala Gln Leu Ser Asp Leu Ser Ser Cys Ser Asp Ile Leu Asp Gly Ser
 195 200 205
 Ser Ser Ser Ser Gly Leu Ser Ser Asp Pro Leu Ala Xaa Xaa Gln Arg
 210 215 220
 Tyr Arg Arg Val Ser Ser Ser Met Leu Gln Phe Met Leu Phe Val His
 225 230 235 240
 Leu Asp Gly

<210> 351
 <211> 248
 <212> PRT
 <213> Homo sapiens

<400> 351
 Met Ala Gln Glu Lys Met Glu Leu Asp Leu Glu Pro Asp Thr Ser Tyr
 1 5 10 15
 Gly Gly Thr Leu Arg Arg Ser Ser Ser Ala Pro Leu Ile His Gly Leu
 20 25 30
 Ser Asp Leu Ser Gln Val Phe Gln Pro Tyr Thr Leu Arg Thr Arg Arg
 35 40 45
 Asn Ser Thr Thr Ile Met Ser Arg His Ser Leu Glu Glu Gly Leu Asp
 50 55 60

361

Met	Val	Asn	Arg	Glu	Thr	Ala	His	Glu	Arg	Glu	Met	Gln	Thr	Ala	Met
65					70					75					80
Gln	Ile	Ser	Gln	Ser	Trp	Asp	Glu	Ser	Leu	Ser	Leu	Ser	Asp	Ser	Asp
			85						90					95	
Phe	Asp	Lys	Pro	Glu	Lys	Leu	Tyr	Ser	Pro	Lys	Arg	Ile	Asp	Phe	Thr
			100						105				110		
Pro	Val	Ser	Pro	Ala	Pro	Ser	Pro	Thr	Arg	Gly	Phe	Gly	Lys	Met	Phe
		115					120					125			
Val	Ser	Ser	Ser	Gly	Leu	Pro	Pro	Ser	Pro	Val	Pro	Ser	Pro	Arg	Arg
	130					135					140				
Phe	Ser	Ser	Arg	Arg	Ser	Gln	Ser	Pro	Val	Lys	Cys	Ile	Arg	Pro	Ser
145					150					155					160
Val	Leu	Gly	Pro	Leu	Lys	Arg	Lys	Gly	Glu	Met	Glu	Thr	Glu	Ser	Gln
			165						170					175	
Pro	Lys	Arg	Leu	Phe	Gln	Gly	Thr	Thr	Asn	Met	Leu	Ser	Pro	Asp	Ala
			180						185					190	
Ala	Gln	Leu	Ser	Asp	Leu	Ser	Ser	Cys	Ser	Asp	Ile	Leu	Asp	Gly	Ser
		195					200					205			
Ser	Ser	Ser	Ser	Gly	Leu	Ser	Ser	Asp	Pro	Leu	Ala	Lys	Gly	Ser	Ala
	210					215					220				
Thr	Ala	Glu	Ser	Pro	Val	Ala	Cys	Ser	Asn	Ser	Cys	Ser	Ser	Phe	Ile
225					230					235					240
Leu	Met	Asp	Asp	Leu	Ser	Pro	Lys								
				245											

<210> 352

<211> 1529

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(1529)

<223> n = A,T,C or G

<400> 352

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gccccttagc ccccgcccc agctgccagt cccagcagc tcagtcctgc agtgagagtc 180
ttgggagtc atagctaagc accaggagct gagcactgcc cgctgtgctt gcctgcaagt 240
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ccctgaggag atccagcagc gctcccctaa tccatgggct cagtgcctt tcacagggtt 360
tccaacctta cacacttaga actcggagga atagtacaac aattatgagc cgtcacagcc 420
tggttaagtat agaagaagaa ggcctggata tggatgaac agaaactgca catgaaagg 480
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362

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gaggaatctt ttttcttagt gcctcaaaaa acacctatct tgagtctata catttaagaa 1320
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<210> 353
<211> 252
<212> PRT
<213> Homo sapiens

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<400> 353
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Gly Gly Thr Leu Arg Arg Ser Ser Ser Ala Pro Leu Ile His Gly Leu
 20      25      30
Ser Asp Leu Ser Gln Val Phe Gln Pro Tyr Thr Leu Arg Thr Arg Arg
 35      40      45
Asn Ser Thr Thr Ile Met Ser Arg His Ser Leu Val Ser Ile Glu Glu
 50      55      60
Glu Gly Leu Asp Met Val Asn Arg Glu Thr Ala His Glu Arg Glu Met
 65      70      75      80
Gln Thr Ala Met Gln Ile Ser Gln Ser Trp Asp Glu Ser Leu Ser Leu
 85      90      95
Ser Asp Ser Asp Phe Asp Lys Pro Glu Lys Leu Tyr Ser Pro Lys Arg
100      105      110
Ile Asp Phe Thr Pro Val Ser Pro Ala Pro Ser Pro Thr Arg Gly Phe
115      120      125
Gly Lys Met Phe Val Ser Ser Ser Gly Leu Pro Pro Ser Pro Val Pro
130      135      140
Ser Pro Arg Arg Phe Ser Ser Arg Arg Ser Gln Ser Pro Val Lys Cys
145      150      155      160
Ile Arg Pro Ser Val Leu Gly Pro Leu Lys Arg Lys Gly Glu Met Glu
165      170      175
Thr Glu Ser Gln Pro Lys Arg Leu Phe Gln Gly Thr Thr Asn Met Leu
180      185      190
Ser Pro Asp Ala Ala Gln Leu Ser Asp Leu Ser Ser Cys Ser Asp Ile
195      200      205
Leu Asp Gly Ser Ser Ser Ser Ser Gly Leu Ser Ser Asp Pro Leu Ala
210      215      220
Lys Gly Ser Ala Thr Ala Glu Ser Pro Val Ala Cys Ser Asn Ser Cys
225      230      235      240
Ser Ser Phe Ile Leu Met Asp Asp Leu Ser Pro Lys
245      250

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<210> 354
<211> 1574
<212> DNA
<213> Homo sapiens

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<400> 354
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<210> 355

<211> 267

<212> PRT

<213> Homo sapiens

<400> 355

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20          25          30
Ser Asp Leu Ser Gln Val Phe Gln Pro Tyr Thr Leu Arg Thr Arg Arg
35          40          45
Asn Ser Thr Thr Ile Met Ser Arg His Ser Leu Leu Leu Ser Ser Ser
50          55          60
Pro Asn Arg Ile Pro Ser Ser Arg Leu His Gln Ile Lys Arg Glu Glu
65          70          75          80
Gly Leu Asp Met Val Asn Arg Glu Thr Ala His Glu Arg Glu Met Gln
85          90          95
Thr Ala Met Gln Ile Ser Gln Ser Trp Asp Glu Ser Leu Ser Leu Ser
100          105          110
Asp Ser Asp Phe Asp Lys Pro Glu Lys Leu Tyr Ser Pro Lys Arg Ile
115          120          125
Asp Phe Thr Pro Val Ser Pro Ala Pro Ser Pro Thr Arg Gly Phe Gly
130          135          140
Lys Met Phe Val Ser Ser Ser Gly Leu Pro Pro Ser Pro Val Pro Ser
145          150          155          160
Pro Arg Arg Phe Ser Ser Arg Arg Ser Gln Ser Pro Val Lys Cys Ile
165          170          175
Arg Pro Ser Val Leu Gly Pro Leu Lys Arg Lys Gly Glu Met Glu Thr
180          185          190
Glu Ser Gln Pro Lys Arg Leu Phe Gln Gly Thr Thr Asn Met Leu Ser

```

364

195	200	205
Pro Asp Ala Ala Gln Leu Ser Asp Leu Ser Ser Cys Ser Asp Ile Leu		
210	215	220
Asp Gly Ser Ser Ser Ser Ser Gly Leu Ser Ser Asp Pro Leu Ala Lys		
225	230	235
Gly Ser Ala Thr Ala Glu Ser Pro Val Ala Cys Ser Asn Ser Cys Ser		
245	250	255
Ser Phe Ile Leu Met Asp Asp Leu Ser Pro Lys		
260	265	

<210> 356
 <211> 4458
 <212> DNA
 <213> Homo sapiens

<400> 356

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365

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<210> 357

<211> 127

<212> PRT

<213> Homo sapiens

<400> 357

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20          25          30
Gly Pro Asp Gln Pro Ala Gly Ser Pro Ala Pro Leu Arg Pro Pro Leu
35          40          45
Pro Arg Thr Leu Arg Leu Arg Lys Tyr Arg Gly Asn Pro Leu Pro Pro
50          55          60
Glu Val Arg Gly Ser Leu Pro Glu Gly Ala Pro Trp Ser Arg Ala Pro
65          70          75          80
Leu Gly Gly His Leu Glu Ala Arg Cys Gly Pro Arg Thr Arg Glu Glu
85          90          95
Arg Ala Ala Gly Ala Ala Ala Thr Ala Gly Gly Gly Ala Gly Ser Pro
100         105         110
Gly Ala Ala Glu Gly Arg Pro Val Leu His Met Leu Pro Leu Gly
115         120         125

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366

<210> 358
 <211> 1168
 <212> DNA
 <213> Homo sapiens

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<210> 359
 <211> 4458
 <212> DNA
 <213> Homo sapiens

<400> 359
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367

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370

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371

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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 September 2002 (19.09.2002)

PCT

(10) International Publication Number
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(51) International Patent Classification⁷: **C07H 21/04**,
21/02

(21) International Application Number: PCT/US02/07826

(22) International Filing Date: 14 March 2002 (14.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

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60/276,026	14 March 2001 (14.03.2001)	US
60/311,732	10 August 2001 (10.08.2001)	US
60/323,580	19 September 2001 (19.09.2001)	US
60/325,149	26 September 2001 (26.09.2001)	US
60/324,967	26 September 2001 (26.09.2001)	US
60/325,102	26 September 2001 (26.09.2001)	US

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(74) Agents: **SMITH, DeAnn, F.** et al.; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
13 March 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NUCLEIC ACID MOLECULES AND PROTEINS FOR THE IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF OVARIAN CANCER

(57) Abstract: The invention relates to newly discovered nucleic acid molecules and proteins associated with ovarian cancer. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human ovarian cancers are provided.



WO 02/071928 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/07826**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) :C07H 21/04, 21/02

US CL :536/23.1, 24.31, 24.33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 24.31, 24.33

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, DIALOG ONESEARCH ovary, ovarian, tumor, cancer, expression, level, marker, RNA, DNA, polynucleotide, oligonucleotide,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,976,799 A (O'BRIEN et al) 02 November 1999, column 2, lines 27-47.	1
Y	US 5,709,999 A (SHATTUCK-EIDENS et al.) 20 January 1998, column 8, lines 38-67; column 15, lines 52-56; column 69, lines 26-30.	1
Y	US 6,087,125 A (BANDMAN et al) 11 July 2000, column 3, lines 15-25.	1
Y	WO 96/05308 A1 (MYRIAD GENTICS, INC) 22 February 1996, page 3, lines 9-17; page 12, lines 2-11; page 21, lines 24-25	1



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

11 JULY 2002

Date of mailing of the international search report

16 SEP 2002

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

STEPHANIE ZITOMER

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/07826

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, SEQ ID NO:1

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Groups 1-198, claim(s)1-198, each drawn to a different method of detecting ovarian cancer.

The inventions listed as Groups 1-198 do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Claim 1 comprises 198 different methods each defined by a different nucleotide sequence each of which constitutes a different special technical feature and therefore a different invention. Thus, there is no single special technical feature in claim 1 nor a single inventive group. PCT Rule 13 permits a product, process of making the product and process of using the product in an inventive group but does not permit multiple methods of the same type in an inventive group